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ANESTHESIOLOGY

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THE PLACE OF THE ANESTHETIST IN AMERICAN MEDICINE *

HOWARD W. HAGGARD, M.D.

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WHAT I have to say here regarding the place of the anesthetist in American medicine is not an encomium either of the men in this field of medicine or of their contributions. I offer no praise of the anesthetist as a scientist or as an humanitarian, nor do I glorify the relief from suffering afforded by his skill and knowledge. If then, I depart, as my negations must signify, from the easy, ingratiating words customarily spoken on occasions of this kind and under a title such as I have chosen, it is with a purpose.

That purpose is not to define the calling of the anesthetist in terms of what has been done and what can be done in the laboratory or at the operating table or at the bedside. It is not the contributions of the anesthetist with which I deal, but instead, the public regard in which these contributions are held. And I shall emphasize the fact that it is this public regard which determines the place of the anesthetist in American medicine.

There are some here among you, perhaps, who feel that your duties as anesthetists are complete when to the individual patient you have given the best anesthesia that modern knowledge affords. Admitting the primary importance of good anesthesia, this view is, nevertheless, to my mind, a limited and a narrow one.

It contributes little to the real advancement of anesthesia. It is not enough that good anesthesia can be given and that it is given to a fortunate few. What is of real importance is that all anesthesia shall be the best that modern knowledge affords. And this desirable end can be reached only when the public recognizes the need and the importance of good anesthesia; and recognizes most of all that the administration of an anesthetic is a major therapeutic operation. It is only with such

* Read at a meeting of the American Society of Anesthetists, Inc., New York World's Fair, New York City, October 12, 1939.

recognition and with such understanding that the anesthetist will receive that public regard and public support which are essential to the fullest development of his calling. And to attain this necessary public recognition, the anesthetist must not only give good anesthesia; he must also shape public opinion.

It is thus a social rather than a medical matter with which I deal. And if, in dealing with it, I skirmish rather than strike to the center, if my views seem philosophical rather than practical, and if I speak in analogy, it is because no one can give direct and simple solutions to social problems. I do not need to call your attention to conditions here and elsewhere to emphasize the fact that our knowledge toward the solution of social problems in any walk of life is meager. You and I cannot solve the social problems of today. But we can recognize some of them and we can try to analyze some of them. And from this analysis there are certain inferences which we may draw at least regarding the social forces which operate in medical progress. Some of these inferences will form the theme of my discussion.

It is obvious beyond question that true progress is achieved in medicine only when two conditions have been fulfilled. The first of these is medical discovery; the medical research which establishes the means by which disease and suffering can be prevented or alleviated. But discovery alone prevents no disease and it alleviates no suffering. Medical discovery without the fulfillment of the second condition is of academic interest only. And this second condition is more of a social than a medical matter. It is application. Application, utilization, in turn, are determined by public regard, public opinion. Such application comes only when public opinion is shaped. The shaping of public opinion is a social matter.

It further has been an obvious fact in medical history, but never more obvious than at the present, that the benefit that could be conferred by any measure of medicine and the extent of the need for it are no direct indications of the regard in which it is held by the public or the extent to which it is accepted and applied. Regard and application come when public view is shaped to an appreciation. No beneficial measure of medicine ever reaches public acceptance and support on the basis alone of laboratory experimentation or clinical investigation. It receives the recognition and support only when the public view is shaped to an appreciation.

And finally, medical regard and public regard go hand in hand. Public opinion is the doctor's opinion. He is a member of the public. Public demand and regard shape the education in our medical schools.

The only common denominator in all these inferences is the shaping of public opinion.

The three inferences are my propositions. Let me now expand and illustrate them. I have in view particularly the situation of anesthesia but my illustrations may take me far afield.

My first proposition is, I repeat: The benefits that could be conferred by any measure of medicine and the extent of the needs for it are no direct indications of the regard in which it is held by the public or the extent to which it is accepted and supported. Regard and application come only when public view is shaped to an appreciation.

More than 300 years ago Paracelsus laid the foundations of chemotherapy. The new branch of therapy obtained public regard through the unfortunate method so characteristic of the efforts of Paracelsus—that of contention. The members of the medical profession and the public as well took sides in violent controversy as the herbalist and mineralist; the followers of Galen and the followers of Paracelsus. The public attention was there but the difficulty lay in the fact that the scientific basis was inadequate. The basis of controversy is too much public opinion and too little fact. Such a situation in time arouses ridicule which forms its own public opinion—such ridicule as that which was once directed at a controversy of this sort with the statement that the patients of the herbalists died of the disease and those of the mineralists of the remedy. As a matter of fact, except for steel in anemia and sulphur for scabies, little benefit to the patient was obtained from the minerals. True, mercury given just short of therapeutic mayhem hastened the disappearance of the secondary manifestations of syphilis, but it had little effect on the tertiary.

And then, three centuries after the time of Paracelsus, Ehrlich introduced salvarsan. This time it was the laboratory and clinical side which was fully developed. This time it was the social side which lagged. Syphilis continued to exist and to exist plentifully in the presence of what was offered against few diseases—a positive method of diagnosis and a specific remedy.

This anomalous situation, in which there was a prevalence of a disease on the one hand, and, on the other, certain means of control, might have continued indefinitely had not, within the last few years, a deliberate drive, with which you are all familiar, been made to break down the barriers. The breakdown was not accomplished by developing better therapeutic methods, or by clinical demonstrations. It was broken down by radio, newspapers, magazines and books and by word of mouth which led to open discussion. It was an effort made in what should be the most cherished privilege of any profession, that of shaping the folkways of our people. We once called it education; we now call it propaganda.

The doctor often looks down upon this shaping of public opinion; he treats it with indifference, with aloofness, and that in spite of the fact that for him, and for the public, it is equally as important as medical discovery. The doctor, I fear, forgets that his calling is a social calling. At times, although he may complain of fees, he seems to disregard the fact that his calling involves not only personal but also broad and fundamental problems of economics—the direct or indirect pur-

chase of his skill at a level comparable with the service he renders. The important feature is the value placed on this service by the public. The value placed by the public is not based on definite and tangible value received; it is determined by the public's opinion of value received. The patient of today too often takes anesthesia for granted as an accepted accessory to surgical operations for which he must pay as he does for the rent of the operating room. In contrast I ask you what would a patient, of say a hundred years ago, faced with an inevitable surgical operation, have paid for the certainty of painlessness? Is it actually any less important to the patient of today who accepts his anesthesia as a commonplace? The often repeated statement that it isn't lack of appreciation but of economic necessity that leaves the doctor's bill unpaid is a sophistry. No one yet has talked of subsidizing the automobile manufacturers because the public appreciates but cannot pay for automobiles. The fact of the matter is that the quite opposite attitude toward the medical fee is a cultivated one—cultivated now to a point when our citizens are beginning to think that medical service for everyone poor and rich alike is to be regarded as a civic contribution like the paved roads. The city pays for the roads but the citizen still pays for his own automobile. It is all, gentlemen, a matter of cultivated public opinion; the establishment of value by the public. And in these matters the modern physician has not influenced public opinion but instead has been influenced by public opinion. He has assumed something of the self-protective attitude of the cloistered research worker, of the austere institutional clinician. He has deliberately assisted the public in cultivating this regard of him. And it is to his detriment and I think to the detriment of public interest.

Public opinion, for good or for bad, is shaped by propaganda. People use one toothpaste, or another, not wholly because of the proven merits of the product, but because of propaganda. Have you ever stopped to think why the public, on the one hand, learns so quickly of any discovery in dietetics, and, on the other hand, so slowly of some medical measure, say the striking benefits of modern scientific anesthesia? The food discoveries are popularized by food manufacturers for commercial interests. Commercial interests know the value of good propaganda. Among them it does not have this euphonism; it is known as advertising. Discover a new vitamin today and tomorrow it will be in beer and bread and the day after the technical terminology of the nutritionist will roll glibly off the tongues of 100,000,000 people. The same 100,000,000 people still regard chloroform as the major anesthetic agent in use and look upon the administration of an anesthetic as something requiring only slightly more skill and professional knowledge than the giving of a dose of castor oil. The members of the medical profession are inclined to believe—at least so their actions would indicate—that the world will pause and eagerly, seriously and intelligently weigh and ponder the best in therapy and will then in sol-

emn decision accept and use it. There is no greater fallacy. The public does not ponder and weigh; in medical matters it has not the knowledge to do so—only the emotions. It takes its opinions fully formed and accepts those which are forced upon its attention. This direction of the public in the shaping of folkways is education, propaganda, advertising—take whichever term suits your taste. Each can have dignity; and each can be a public service.

Before my digression on publicity I had in a few sentences recapitulated the progress made in one branch of chemotherapy to essential completion—from discovery to application. Let me outline now some steps in the progress of anesthesia.

First there was the great discovery of principles. Here are the stories that are familiar to you and even becoming familiar to the public. They are those of nitrous oxide and ether and chloroform—Davy, Long, Morton, Wells and Simpson. The sum total of the propaganda value of these stories is that anesthesia is available; that there are drugs which give a blessed relief from pain. The sum total of public opinion formed is that it was unpleasant to have an operation before the days of anesthesia. This was very useful propaganda 90 years ago when the principle of anesthesia was under criticism. Today it is about as useful as is propaganda in favor of the principle of utilizing medicaments or surgery or having hospitals or trained nurses. Propaganda which deals only with principles now accepted, obscures the one feature of anesthesia which is of importance to the public today—that is the administration of anesthesia.

The second era in the progress of anesthesia was the search for new anesthetics. This was led, as you know, by Simpson with the discovery of chloroform. It is true that Simpson did a yeoman's service in shaping public opinion in his forceful pamphlets justifying the use of the principle of anesthesia. But chloroform was a long time ago. Since then we have seen the new anesthetics multiply in number and in professional usefulness. But these things are wholly the technical equipment of the anesthetist. They permit him to give better anesthesia but they mean little in creating public opinion. It is not the anesthetic agent which should be held up for public interest, but the administration of the anesthetic.

We have lived through the period of apparatus. We have seen the towel on a wire mask give way to a complicated respiratory apparatus with delicate controls. But again this means little to the public except that in the increasing number of moving pictures showing surgical operations, it is evident that the patient is still alive when the rubber bag fills and empties rhythmically and the valves jingle. In such pictures which express public views and public regard the anesthetist is a handsome nurse, or, lacking this appeal, he is obscured beyond the frame of the picture so that the surgeon may have the center of the stage.

And gentlemen, it was not the invention of a new antiseptic, of a new scalpel, or a new operating table that gave the surgeon—I speak collectively—the prestige and pre-eminence which he enjoys in public regard. This prestige gives surgery a prominent position in the curriculum of the medical school. It draws many of the better students into this field.

Today—to my mind at least—where the anesthetist, and again I speak collectively, is weakest, is in this very social aspect; this matter of prestige. The analysis of prestige and its importance brings me to the last of the propositions which I postulated: Medical regard and public regard go hand in hand. Public opinion is the doctor's opinion. He is a member of the public. Public demand and regard shape the education in our medical schools. And I may add that the public regard in which a branch of medicine is held is no direct measure of the benefit derived from that branch of medicine. It is a measure of the shaping of public opinion.

In broadest terms what I am saying is that throughout the ages the respect in which the doctor was held, the veneration bestowed upon his calling, and the support given to him have had absolutely nothing to do with the benefits the doctor and his calling have conferred upon the public. The regard given him is a cultivated regard; it is a fortunate coincidence when he deserves this regard.

Let me support my point with generalities. Look back, if you will, at the medicine man of uncivilized people; from our point of view all that he possessed was a bag of tricks in psychotherapy, and a few empirical methods of drug therapy, and yet he was held by his people in a veneration that amounted to actual awe. He was the great leader of his people.

Look next at the physician of the late Middle Ages and the Renaissance. He had far more to offer than the savage, but nevertheless he was regarded with no veneration. He was a menial. The surgeon was a barber.

And then look at the physician of the late 18th century, particularly in this country. That was a period in which men's minds were turned to serious matters. Devotion to principle was characteristic of the day. Public-minded, socially-minded men devoted their services to the needs of their fellow men with an almost religious enthusiasm; they were in medicine and they were in public affairs. They followed medicine as a duty of service to their fellow men; they signed the Declaration of Independence. They may—and often did—commit therapeutic outrages on their patients. You will recall Rush's famous 10 and 10; 10 grains of calomel and 10 grains of jalap at a single dose, often with copious bleeding. But he and his brethren were regarded with the highest respect. Their position in the public mind was far higher than that of the physician of today, in spite of the fact that what they had to offer as science was negligible.

You remember that famous remark of Dr. Benjamin Rush when he expressed his regard of science. He said "Medicine is my wife and science my mistress." You may remember, too, the waspish comment a half century later of Oliver Wendell Holmes when he said: "Medicine may have been his wife and science his mistress, but this breach of the seventh commandment cannot be shown to have been of any advantage to the legitimate recipient of his affections."

I bring in this anecdote because it shows more clearly than any words of mine the tendencies of the times. Holmes, present on that day when anesthesia was first publicly demonstrated, came in the era when science was beginning to dominate medicine—when the whole problem of the ills of mankind was to be solved by science and science alone. The laboratory and the clinic rather than the public place were to become—and then did become—the retreats of medicine. The door closed on the doctor. He was engaged, it is true, in a fundamental feature of his profession—the accumulation of knowledge. But it was to the exclusion of an equally fundamental feature—the shaping of public opinion to the full application of that knowledge.

In consequence of his sequestration a mode of thought was created. It was one which put the premium on medical discovery and not on medical application. In the last hundred years, with the introduction of the exact sciences into medicine, medical research has yielded some of the most beneficial knowledge that the human race has ever acquired. Enthusiasm has grown high and the mode of thought crystallized. The beginning and the end of medicine seemed to be research; the finding of new and better ways. And that, unfortunately, in the disregard of the fact that discovery without application is only of academic interest. It was a miserly method; the accumulation of valuables without putting them into circulation. The social side, the equally dignified propaganda side of medicine, was largely ignored, or, if not ignored, handled so badly or with such indifference as to fail in its purpose. It was treated with contempt as below the dignity of the doctor.

Now I speak feelingly on this subject and for a personal reason. I am, by sheer chance, a research worker; a laboratory man. But ten years ago I held much the same idea that I hold today regarding the need of propaganda although my views have changed considerably on how it should be done. At that time I was offered radio facilities to talk on such subjects. To the possible disadvantage of my professional career, I rather unwisely accepted.

For a little over a year I continued to talk with considerable criticism from some of my scientific confreres. The criticism did not come because of the amateurishness of my talks—and they were amateurish—but because such work was not consistent with a scientific career. So pressing was the criticism that I felt it then advisable to stop. That was ten years ago. In the intervening years conditions have changed. Medical radio propaganda of a similar sort—mostly rather bad in exe-

cution and misdirected I fear—has now become reasonably respectable. Time on the radio is eagerly sought by many medical societies. This year, to my amusement, the talks I gave with only a meager knowledge of the principles of propaganda ten years ago are now being repeated nearly verbatim by six different medical groups which have been given radio time. The certain conclusion that one must draw is that, while the principle of propaganda has been given some respectability, the method of carrying it out has not correspondingly improved.

In these rather personal digressions I have wandered from the point I was trying to make that public opinion is shaped by social endeavor and not by laboratory and clinical discovery. I have spoken in generalities. Let me next trace out along a somewhat different line a specific example of the development of prestige and the importance of prestige to the advancement of any branch of medicine. I turn to the surgeon. Incidentally I shall speak only of the advantages of prestige and deal with none of the disadvantages, the most obvious of which is the scramble of the mediocre toward the specialty which at the moment enjoys prestige.

As you are all aware, the surgeon did not always have prestige with the public or even the reasonable respect of his medical associates. In this regard there is a most pertinent and illuminating line in that ancient ritual which we call the Oath of Hippocrates but which in reality was the more ancient oath of the medical priests in the Temples of Aesculapius. It says, in effect: We, as respectable physicians, swear not to cut for the stone but to leave this to men who do such things. This stricture was not directed at the urologist, but at the surgeon. The surgeons were the men beyond the pale of professional respectability who did such things. Such was the attitude toward the specialist in surgery in the classical period of medicine. It was not one of great prestige. And it sank distinctly lower during the subsequent Arabic period of medical supremacy. Surgery was menial work; the professional standing of the surgeon was something comparable to that of the hospital orderly of today.

This regard of the surgeon carried over into Europe. No clearer indication of the prestige, of the recognition, or the reverse, of the importance of any field of medicine by the public, is to be found than in the curriculum of the medical school. In the early great medical schools of Europe no surgery whatever was taught. You will remember that Ambroise Paré, the 16th century Father of French surgery, was a barber. Only royal insistence obtained for him a grudging recognition by the medical men of the period. You may have read his Surgery and you may have read one of the standard medical textbooks of that day. If you have, you will see that Paré with his surgery had far more to offer than the internist with his comparatively greater prestige. All the physician had, as contrasted with the surgeon, was a more scholarly social distinction in the eyes of the public. Yet this public opinion was

sufficient to literally abolish intelligent surgery. By the time of Louis XIV, Paré's surgical knowledge had actually been so far forgotten that when the king developed a fistula in ano none of his attending medical men knew how to perform the necessary operation. It required six months study and preparation in a veritable medico-surgical comedy before the operation was performed on the royal posterior. This incident brought royal favor to surgery. Royal favor brought public regard with a revival of surgery. Of such things, gentlemen, is prestige created.

And I may add, parenthetically, that this was not the only specialty of medicine which profited by royal example. Obstetrics made its first stride toward social acceptance when Louis XIV had a male midwife for the confinement of Lovalliere. You all recall the public opinion created in favor of anesthesia by Queen Victoria's acceptance of chloroform at the birth of Leopold.

A sounder but no more effective prestige than that of royal favor was given to surgery by John Hunter when he introduced surgical pathology. This step made the surgeon something more than a technician who clipped off legs or arms and tied up aneurisms. It brought in surgical diagnosis. Surgical diagnosis required something more than manual dexterity. It required intelligence and education. A surgeon of the times, which was only about 150 years ago, said that John Hunter had made the surgeons gentlemen. This surgeon, in his statement, did not mean that the men of his calling had gained prestige with the whole public, but only with that part of it represented by the physicians. It meant that after the long struggle the surgeon might stand on a level with the physician and that the curriculum of the medical school would, in consequence, include a fair proportion of surgery. The public prestige of surgery followed. Inseparable to its development were the discovery of anesthesia, antisepsis and asepsis, the founding of trained nursing and the rise of the modern hospital. Anesthesia and antisepsis were taken as adjuncts to surgery; trained nursing originated and grew as surgical nursing; and the modern hospital was built to house surgery. The public saw these things, the public recognized the spectacular success of surgery; and surgery became, in public regard, the prodigy of medicine. Public prestige meant large fees; large fees, plus prestige, meant a flood of students seeking surgical training; this demand further influenced the curriculum of the schools. And as a final advantage, surgery was personal. As a branch of medicine it has done far less toward modern health and longevity than has sanitation, but sanitation lacks prestige because it is impersonal. From the World War there came a score of books of surgical reminiscence for public consumption. There was not more than one that I know of on sanitary reminiscences. And yet the benefits conferred by sanitation were profoundly greater than those of modern surgery.

As I understand it, the sound, enduring establishment of any specialty of medicine is predicated upon three major points:

1. It must be an intellectual as well as a manual occupation.
2. It must receive respect and prestige from the other members of the medical profession. This respect may come primarily from the doctor as it did in surgery, or it may follow public opinion.
3. It must have public comprehension and must receive public respect and prestige. In short, it must appeal to the public.

Most sketchily I have traced out these steps in surgery. Let me apply them in turn to anesthesia. Anesthesia is new and anesthesia got off to a bad start from its very beginning. There was for years in anesthesia no intellectual or scholarly basis; it was a technical procedure carried out by rule of thumb by men or women who had no special knowledge of the respiratory and circulatory physiology and of the pharmacology that today are the primary requirements of the professional anesthetist. Anesthesia was the giving of a dose of medicine. The dose could be administered by the nurse or interne and, in an emergency, by a layman. A good many patients survived this sort of anesthesia. For that matter, a good many patients survived surgery before the days of Lister. Moreover, anesthesia was rarely, if ever, administered without accompanying surgical procedures and those were the days of rapid traumatic surgery. It was difficult to separate the risk of one from the risk of the other. Surgery was recognized and accepted as a hazard. But less well recognized was the fact that bad anesthesia often added immeasurably to the hazard of surgery—not the risk on the operating table of death from anesthesia, but that of subsequent failure hours or days after the operation was completed. In the maze of variables the part played by bad anesthesia was obscured.

I speak feelingly of bad anesthesia of the not very remote past—and there is still much—for I was once, for a short time, an anesthetist and a very bad anesthetist. During my internship I was trained by a nurse. I was given a cone, a can of ether and a few empirical tricks. The memory of those days had a salutory effect on me. In later years when it came time for me to undergo an operation—a tonsillectomy—my first thought was to obtain the services of the best anesthetist I could find. The second, and very secondary, was to find a throat specialist. Any good operator—and there were dozens at hand—could do a safe and competent tonsillectomy. But anesthesia, possibly because of my early experience, possibly because I was a respiratory physiologist, was a serious matter. It was a major therapeutic procedure without regard for the significance or insignificance of the operation. That is a point that the public does not appreciate nor, for that matter, some members of the medical profession.

If the members of the medical profession at large held such convictions, then the teaching of the principles of anesthesia would not, in some otherwise good schools, be crowded into physiology and pharma-

cology and its clinical aspects dismissed with a few demonstrations. It would be taught, as it should be taught, and I hope soon will be taught in every school, so that every medical student would leave the school with a beneficial and practical knowledge of respiratory and circulatory physiology which most do not get; and with an appreciation of the vast fund of knowledge and of the judgment that the good anesthetist must possess. If he did obtain these things which seem so essential a feature of a medical education he would carry with him a high regard for the specialty of anesthesia. If the members of the general public shared such views regarding anesthesia—and they are perfectly willing to share them if they are told of them—the anesthetist would come into his rightful position.

Thus, gentlemen, it seems to me that the future position of the anesthetist in American medicine is largely a matter of social change. The anesthetist will not establish his position by laboratory and clinical research alone, or by the development of new anesthetics and new apparatus. He will establish it only when he deals with the important but often neglected social feature. Even in spite of this neglect by most anesthetists the fact remains that the anesthetists have, during the last decade, made more progress toward establishing their specialty than has any other group in the profession. So far the progress has been mainly from within. It has been organization, the founding of journals and sections and the insistence on better teaching of anesthesia. And I do not need to tell you here that for this progress you owe a great debt to one of the most socially-minded and certainly one of the bravest men I have ever met—Dr. F. H. McMechan.

And now, in conclusion of this rather discursive and rambling talk, I am going to assume that you agree, at least in part, with my views. And in so assuming, I am going to presume so far as to offer some practical suggestions.

The first of these is that propaganda does not mean of necessity great radio programs, magazine articles and books. They are vastly helpful. But the first step is an earnest conviction on the part of the anesthetist of the importance of his calling and with this conviction an enthusiasm to tell of it by word of mouth to those with whom he comes in contact. Word of mouth may be slow, but it is the soundest propaganda there is. If the efforts toward shaping ideas go on further to public talks and magazine articles, then do not fall into the common fault of dramatizing discovery. Dramatization is emotional and sound social points cannot be put over in a setting of emotions, only conflict and fear. There is no need of arousing interest; the public already has an avid interest in all medical matters. Discovery alone so often emphasized in medical propaganda is not the feature to bring pointedly before the public. Discovery is medical research; it belongs to the doctor. The public plays no part in it except possibly to provide funds. The point to emphasize is application. What good does it do anyone to

announce over the radio, and in the papers, that a new anesthetic has been discovered? The announcement provides only table talk for the members of the public. It leaves no impression of the importance, the skill, the knowledge, of the man who must administer the anesthetic.

Today the public, by and large, believes that the important decision in anesthesia is what anesthetic they will be given, or possibly what method will be used. When, by propaganda, you have changed this view to one in which the important decision is what man shall give the anesthetic, then the problem of the place of the anesthetist in American medicine will be solved.

A Section on Anesthesiology was established in the American Medical Association during its Ninety-First Annual Session, which was held in New York City, June 10–14, 1940.

CYCLOPROPANE ANESTHESIA [1]

ARTHUR E. GUEDEL, M.D.

Los Angeles, Cal.

THIS report is based upon clinical observations during the past eight years of more than eight thousand anesthesias. Included are cases of Drs. D. N. Treweek, C. F. McCuskey, the author and our associates.

The subject will be discussed under four subtitles, namely: Controlled Respiration, Cardiac Arrhythmias, Abdominal Relaxation, and Technic.

CONTROLLED RESPIRATION

This involves the consideration of apnea and artificial respiration by rhythmic pressure upon the breathing bag. Actually it means that the anesthetist deliberately takes the function of pulmonary respiration from the patient into his own hands. This sounds formidable. As a matter of fact, it is simply the physio-pharmacological control of the respiratory center, just as we control by physio-pharmacological means the abolition of consciousness, pain and reflex response during any anesthesia.

Apnea during anesthesia may be produced in two ways. The threshold of response to the stimulus present within the body may be elevated to such a degree that the stimulus present can no longer activate the respiratory neuromechanism; or the physiological stimulus may be depleted to such an extent that it is incapable of activating the function. The threshold of activity of any function is variable. Respiratory threshold may be elevated by hypoxia, and by various drugs, such as opiates, barbiturates, or other anesthetic agents. This elevation is in proportion to the concentration of the drug or to the degree of hypoxia. The normal physiological stimulus of respiration, carbon dioxide, may be depleted so that, even with a normal, or subnormal threshold, respiratory arrest obtains. Control of pulmonary respiration depends upon the relationship between threshold and stimulus under all living conditions. When stimulus falls below threshold, there is respiratory depression or some degree of respiratory paralysis. When stimulus rises above threshold, there is hyperpnea in increasing proportion with the elevation of stimulus. Conversely when threshold rises above stimulus there is respiratory depression depending upon the degree of elevation of threshold and when threshold falls below stimulus, hyperpnea increases in proportion to the degree of fall of threshold.

[1] Read before the Joint Meeting of the American Society of Anesthetists, Inc., and the Pacific Coast Association of Anesthetists, December 14, 1939, Los Angeles, California.

Respiratory stimulants may act either by increasing the irritability of the respiratory neuro-mechanism, lowering of threshold, or by increasing the carbon dioxide content of the blood, elevation of stimulus, or by a combination of these circumstances. Because of lack of space this discussion of fundamental principles of controlled respiration has been epitomized.

Apneas During Cyclopropane Anesthesia

Cyclopropane is a potent respiratory depressant. It is capable of elevating the respiratory threshold to such a degree that the respiratory neuro-mechanism cannot be activated by any known stimulus. The degree of elevation of threshold is in direct proportion to the concentration of cyclopropane. Roughly speaking, for illustration, a concentration of twenty to thirty per cent. of cyclopropane in the inspired atmosphere may elevate threshold beyond stimulus, and apnea will occur. With this concentration the respiratory neuro-mechanism may usually be activated by adding carbon dioxide to the anesthetic mixture. The concentration of cyclopropane may be increased beyond this point to the neighborhood of seventy-five per cent. without evidence of anoxia, in which case, as stated above, threshold will be entirely out of reach of any known stimulus. Then the only way in which respiration can be re-established is by decreasing the concentration of cyclopropane in the blood to a point where irritability of the respiratory neuro-mechanism is restored, or threshold is lowered to a point where it is again within reach of stimulus.

Carbon Dioxide During Cyclopropane Anesthesia

Because of the controversial aspect of recent discussions of the effects of carbon dioxide during anesthesia, it becomes necessary to state our views in this matter. We consider carbon dioxide a physiological product necessary to normal life, just as are adrenalin, thyroxin, pituitary extract and gastric juice. Any decrease or increase in the production of carbon dioxide within the body will give rise to characteristic symptoms, just as will any of the other above mentioned products. Presence of too much or too little of these products including carbon dioxide may be lethal. However, within reasonable limits they all have therapeutic value. In our experience, these reasonable limits are unusually wide in the case of carbon dioxide.

Until recently it was believed that thirty or thirty-five volumes per cent. carbon dioxide in the body represented the low point of irreversibility. However, Seevers, et al. (1), have reduced carbon dioxide tension in arterial blood in dogs to as low as twenty-one volumes per cent. with no apparent permanent harm. The safe latitude of permissible increase in carbon dioxide above normal is much narrower. Therefore, more care must be exercised in watching for increased than for de-

creased content of carbon dioxide during anesthesia. It is impossible to establish any safe upper limit of concentration for the carbon dioxide within the body, just as it is impossible to establish any safe upper limit for any drug in all individuals. The answer lies in the degree of irritability of the central and autonomic nervous system at the time.

An excess of carbon dioxide in sufficient amount usually produces generalized convulsions. It is not improbable that convulsions reported as being due to ether anesthesia, are in reality due to an excessive accumulation of carbon dioxide. Tolerance for increase of carbon dioxide depends upon the individual. Convulsions are most likely to occur in sthenic febrile patients, and particularly in febrile children. They are least likely to occur in the aged or asthenic types. In other words, it may be assumed that tolerance for an excess of carbon dioxide is increased as the metabolic rate at the time is decreased.

A recent report by Humans (2) described a tracheal tug as one of the signs of third plane, third stage ether anesthesia. This tracheal tug is probably not a sign of third plane, third stage ether anesthesia, but is likely a premonitory sign of convulsions associated with an excess of carbon dioxide. With cyclopropane anesthesia, employing the apneic technic, this tracheal tug which is easily felt between the chin and the larynx by the fingers of the mask-holding hand, is synchronous with inspiration, or what might be the inspiratory period of passive respiration. It has appeared with such regularity when there is inadequate pulmonary ventilation that we have come to associate the two. With relatively fresh soda lime we have been able to abolish tracheal tug by immediate pulmonary hyperventilation. Although the discussion of tracheal tug is a bit foreign to the subject of this paper, I would call attention to it now as a fairly good sign of approaching convulsions. Its appearance calls for an immediate rapid reduction of the concentration of carbon dioxide in the blood.

CARDIAC ARRHYTHMIAS

We have been employing our present technic for eight years. Until the past two years, we thought nothing about cardiac arrhythmias during cyclopropane anesthesia. We knew they existed, but were not worried because the patients seemed in good condition regardless of the depth of anesthesia and the quality of the pulse. Some eighteen months ago, we began to realize that we must do something to protect ourselves against the great fear that present day teaching was building up regarding these arrhythmias. The first move was to adopt the habit of fixing a pre-cordial stethoscope upon each patient. We learned much from this practice. However, for perhaps two years before precordial application of the stethoscope we were using the "arteriolar-capillary-refill-time" as one of our chief means of determining circulatory efficiency.

This "A-C-R" as we have come to call it, although of no value as a sign of depth of anesthesia, has become one of our most sturdy columns of support in the estimation of circulatory efficiency.

An area upon the forehead is blanched by pressure of a finger, and the rapidity of refill of this area with blood is noted. This refill time remains the same regardless of depth of anesthesia. It slows perceptibly in the presence of hemorrhage or of surgical shock. There is some variation in the A-C-R time in different individuals. The rapidity of refill of the blanched area should be determined at the beginning of each case, and used as a criterion of circulatory efficiency throughout anesthesia. The arteriolar-capillary-refill time varies in different cutaneous areas. For example, in the neighborhood of the clavicles and upper thorax it is much slower than upon the forehead. The time is somewhat shortened on the forehead when the patient is in deep Trendelenburg position. It is also shortened by pressure of mask-holding head straps which might obstruct venous return.

We may assume that peripheral blood supply to the head and brain is greater than to the skin under ordinary circumstances. Therefore, with a satisfactory A-C-R time of the forehead in the presence of a good cutaneous color, we consider the patient to be in a satisfactory circulatory condition regardless of the pulse as felt by the fingers. We have learned from the University of Wisconsin that there are cardiac arrhythmias associated with all types of inhalation anesthesia, as determined by the electrocardiograph (3), and that these arrhythmias, so determined in the dog, are less with cyclopropane than with ether and chloroform (4). We have also been taught that cyclopropane is toxic to the heart in the same manner as is chloroform (5). From our experience it is my belief that this is not true. It is true that both cyclopropane and chloroform increase the irritability of cardiac conductive tissue to the action of adrenalin. At that point, however, cyclopropane stops, whereas chloroform has a further or another action, of direct toxicity to the cardiac musculature.

The question arises "Why cardiac arrhythmias?" The answer is yet to be determined. From our observations it would seem that cardiac arrhythmias are reflex in origin and are subject to the same influences as any other reflexes during anesthesia. The electrocardiograph will reveal many arrhythmias which no doubt carry the incidence with ether and chloroform above that of cyclopropane. During many years of experience with chloroform and ether in all stages of anesthesia, cardiac arrhythmias due to anesthesia have attracted but little attention. Palpable arrhythmias under chloroform and ether usually represent a true state of circulatory deterioration, whereas palpable arrhythmias under cyclopropane do not.

We must consider circulation, so far as anesthesia is concerned,

merely as an intermediate stage of respiration. Adequate oxygenation of the tissues and adequate removal of carbon dioxide is all that we expect from circulation. We, therefore, consider circulation in terms of minute volume rather than output per systole, and we assume that, to repeat, if the patient's color is good and the A-C-R is within normal limits, the circulatory volume is ample so far as oxygenation of tissue is concerned. Regarding the adequate transportation of carbon dioxide away from the tissues, it might not be ample.

There is no evidence of histotoxic anoxia with cyclopropane such as we probably have from chloroform and ether. This observation is based upon the general good condition of patients during and following cyclopropane anesthesia.

Allocation and Classification of Arrhythmias

Allocation of cardiac arrhythmias with relation to concentration of cyclopropane is easy. Classification of types of arrhythmias with relation to concentration of this gas is more difficult and aside from a few observations we have been able to do nothing. The arrhythmias occur at about the point of apnea, with a probable concentration of twenty to thirty per cent. of cyclopropane in the inspired atmosphere and continue until the concentration has reached from forty to seventy per cent. They are most likely to occur in sthenic or neurotic individuals between the ages of puberty and about fifty years. We have had but little opportunity to study these arrhythmias in children.

The width of the arrhythmic range varies to a great extent. The individual whose nervous system is not unusually disturbed will have a narrow arrhythmic range, and in this individual we are able to get beyond the range with a concentration of gas of, let us say, forty per cent. On the other hand, in the extremely neurotic patient a much higher concentration is required to get below the arrhythmic range. We have failed to get below the arrhythmias in a few cases, which fact was probably due to lack of necessity or lack of courage.

Arrhythmias are much more apparent with ascent from deep anesthesia than they are with descent into deep anesthesia. This, as pointed out by Nosworthy (6), may be explained upon the basis of the oil-water solubility ratio of cyclopropane which is 34–1. All cyclopropane transported to and from the tissues must pass through blood plasma, and so far as the oil-water solubility ratio is concerned, blood plasma is little more than water. Descent into deep anesthesia, using high concentrations of cyclopropane, is extremely rapid. During ascent from deep anesthesia, a longer period of time is required to traverse the arrhythmic area, and therefore more arrhythmias are detected.

Aside from an almost constant bradycardia with rapid induction and to a less extent rapid deepening of anesthesia later, we have not

found a definite sequence in the occurrence of various types of arrhythmias. In the arrhythmic range, anything may happen at any time, from simple blocks and extrasystoles to extreme tachycardia. It must be noted in this connection, that without electrocardiographic tracings, there is no way in which we can make a positive diagnosis of ventricular tachycardia. We regard a pulse rate of more than two hundred, as heard through the stethoscope, as ventricular tachycardia. We do not retreat from these tachycardias unless we have ample abdominal relaxation to permit the lightening of anesthesia. If we have a tachycardia without ample relaxation as we regard relaxation, we do not hesitate to increase our concentration of cyclopropane, with the usual result that the tachycardia disappears. Casting a doubt upon our previous statement that anything might happen at any time, we must say that we have not entered or left a tachycardia without passing through some other types of arrhythmia.

The duration of tachycardia varies. They may last continuously from a few seconds to a half a minute. Then, following an interruption by various other types of arrhythmias, they may repeat, and repeat again, so long as we maintain anesthesia at that particular level. During the administration of cyclopropane, the only arrhythmias of serious nature are ventricular fibrillation and complete heart block. We are taught that with increasing concentration of this gas, the cardiac pacemaker is displaced progressively downward from the SA to the AV node, thence through the Bundle of His and the branch bundles to the cardiac conductive tissue, and that the next phenomenon will be ventricular fibrillation. The fact that we drive anesthesia down through the arrhythmic area to a regular pulse, causes us to reject this teaching.

We wish to emphasize here the fact that we fear a combination of hypoxia and deep cyclopropane anesthesia. We have never found it necessary in clinical anesthesia to tolerate hypoxia.

Control of Arrhythmias

You may ask, "If these arrhythmias offer so little trouble, why worry about their control?" The answer, of course, is that we do not yet have a full understanding of the etiology and mechanism of cardiac ventricular fibrillation or of complete heart block. With our present knowledge we feel that either is more likely in the arrhythmic range than above or below it. Inasmuch as we may have to traverse this arrhythmic range from two to four times, we feel that any protection that can be had against arrhythmias will be worth while. To secure protection in this respect we have tried oral medication with the various opiates together with atropine or scopolamine, and various barbiturates. We have tried atropine alone and morphine alone, and we have conducted a number of anesthesias without premedication. None of

the above trials netted anything. Then came the wife of a good surgeon friend who was afraid of anesthesia. Upon request anesthesia was induced with intravenous evipal and, with the pre-cordial stethoscope in place, throughout a deep anesthesia lasting for almost an hour, there were no arrhythmias. Following this we found that intravenous barbiturates administered to the point of complete narcosis, immediately preceding cyclopropane anesthesia, provided protection against arrhythmias in varying degrees. In this work we have used evipal, pentothal, and nembutal in a sufficient number of cases to enable us to make the following classification.

Considering total abolition of cardiac arrhythmias as represented by one hundred per cent., these three barbiturates qualify as follows: (1) Nembutal afforded about sixty per cent. protection. In testing with this drug we hoped, because of its slower destruction within the body, for prolonged protection. The protection that it afforded proved to be both inadequate and too prolonged. (2) Pentothal afforded about ninety per cent. protection. However, its action was short. (3) Evipal affords about eighty per cent. protection and its action was longer than that of pentothal. Inasmuch as the degree of protection afforded against these arrhythmias by evipal was so close to that of pentothal, and of slightly longer duration, we have adopted evipal as the protective agent. With evipal administered intravenously, anesthesia is induced exactly as if no other agent were to be used, usually from .6 gram to 1 gram being injected. A pharyngeal airway is then inserted and cyclopropane anesthesia is induced exactly as if no evipal had been given. It is worthy of note here that the laryngeal reflex is greatly obtunded following the administration of evipal and, in many instances, the laryngeal airway simulates that of an endotracheal anesthesia.

Because of Lundy's (7) teachings in the use of intravenous barbiturates, we have not employed these agents in children. Neither have we employed them for patients over fifty or sixty years of age except in sthenic or extremely neurotic individuals. Above these ages, even without intravenous barbiturates, arrhythmias are minimal.

To make a rough classification of the types of patients in which induction with intravenous barbiturates is advisable, we would say it is indicated for those between puberty and fifty or sixty years of age, in sthenic or nervous individuals, and especially in the presence of febrile reaction. Although we consider this method of induction of more importance in abdominal surgery, we apply it for all nervous patients because of its effect in elevating the threshold of activity of the autonomic nervous system and the conductive tissue of the heart.

ABDOMINAL RELAXATION

Abdominal relaxation that is considered "adequate" varies in different communities and with different surgeons. However, a surgeon who has been operating for a period of time with adequate abdominal

relaxation will tolerate nothing but that. By adequate abdominal relaxation I mean such as is present with perfect spinal anesthesia. Let us compare the abdominal relaxation possible with ether, spinal and cyclopropane. Ether administered to produce a depth of anesthesia where relaxation is comparable to that of spinal anesthesia will destroy muscular tone. This interferes with the constriction of the intermuscular vascular beds and lessens muscular support in the arterial walls, all of which leads rapidly to shock. Spinal anesthesia produces total abolition of traumatic reflex response, but does not destroy muscle tone. Cyclopropane is capable of safely producing total abolition of traumatic reflex response, just as is spinal anesthesia, without abolishing muscular tone.

TECHNIC

As previously stated, we have employed this technic almost without change, during the past seven or eight years. One question is "Which is safer; slow or rapid induction?" The answer to this lies in the etiology or the mechanism of ventricular fibrillation and complete heart block. If these are more likely during light anesthesia, then rapid induction is safer. If these are more likely under deep anesthesia, then the slow induction is safer. We believe that they are more likely under light anesthesia, and that cyclopropane is not directly toxic to cardiac muscle. The faster we can abolish consciousness, the less adrenalin will be thrown into the blood stream during induction. Inasmuch as it is agreed that cardiac arrhythmias depend upon the combination of excess adrenalin and cyclopropane, it behooves us to keep either the output of adrenalin at a minimum or to elevate the response threshold of the autonomic nervous system as much as possible during induction of anesthesia.

The basis for our attitude in this matter of rapid induction is as follows: A fifty per cent. concentration of cyclopropane is not irrespirable, and in properly premedicated patients, not uncomfortable. The circulation from the lungs to the brain is extremely voluminous. There are approximately four liters of air in the lungs of the average adult. The time required for all of the blood to pass a given point is slightly more than a minute but travel from the lungs to the brain occurs in only a few seconds.

We employ a breathing bag of four liters capacity, into which, for induction, we put approximately two liters of cyclopropane and two liters of oxygen. This cyclopropane in a concentration of fifty per cent. when diluted with the four liters of air in the lungs, becomes approximately twenty-five per cent. This is carried rapidly to the brain and consciousness is lost usually in from three to six inspirations. Frequently, apnea occurs at this point. Unless more cyclopropane is added to the breathing bag, this apnea is dissipated within one-half to one minute by circulatory equalization of the gas within the body.

If the operation does not require muscular relaxation, no more cyclopropane need be added until swallowing or movement occurs. However, we do not wait for swallowing or movement but after a minute or so we add another liter or two of cyclopropane, depending upon the type of patient. From this time on, cyclopropane is added in quantities of one-half to one liter as indicated by the state of respiratory activity. This is for surgical procedures requiring little muscular relaxation.

In considering the necessity for addition of cyclopropane after anesthesia is established, we must take into account three items: (1) The high oil-water solubility ratio of 34–1 permits the body fats to accumulate much of the cyclopropane from the blood stream and brain. During the first minutes of anesthesia, with the diffusion gradient steep from the lungs to the fats, this reaction is of considerable consequence. Later in anesthesia, when the diffusion gradient between lungs and fats has become more nearly level this factor diminishes in importance. (2) The release of nitrogen from the tissues and blood to the lungs, so important in nitrous oxide and ethylene anesthesia, is of little consequence because of the potency of cyclopropane. (3) The passage of cyclopropane into and through the wall of the rubber breathing bag is rapid, about the same as carbon dioxide. From a clinical standpoint, this is of no consequence. However, because of these three factors, considerable cyclopropane must be added, particularly during the earlier part of anesthesia, to maintain a constant level, regardless of the depth of anesthesia.

In operations which require little or no muscular relaxation sufficient reflex obtundation for quiet anesthesia is to be had with a normally active respiration. For surgical procedures within the abdomen the picture is different. Although the induction is the same as for extra-abdominal procedures, anesthesia is carried down by passive respiration, without waiting for the dissipation of apnea occurring during the induction. This increase in depth is achieved in the sthenic individual by emptying the breathing bag after about a minute, and refilling it with what we call a 3–1 mixture; that is, three liters of cyclopropane and one liter of oxygen. After two or three minutes this is repeated and if necessary, after two or three minutes more, it is repeated again. Unless the abdomen is sufficiently relaxed it is repeated again and maybe again. All of this gas is administered by passive respiration. With this mixture, which is approximately seventy-five per cent. cyclopropane, and with our continuous flow of oxygen at what we are sure is above metabolic requirements, we feel safe in refilling the bag as often as is necessary to secure adequate abdominal relaxation. Although even for sthenic individuals not more than four or five repetitions of filling the breathing bag are required, we have, for some of our patients under study, during a period of about one and one-half hours, repeated this procedure as many as eighteen

times. The criterion for the number of repetitions of this maneuver is the degree of abdominal relaxation required.

To present, as an illustration, the conduct of cyclopropane anesthesia for an ordinary hysterectomy, induction would be with a 2–2 mixture, that is, two liters of cyclopropane and two liters of oxygen. After a minute, a change to a 3–1 mixture, and after two or three more minutes, another change to a 3–1 mixture is made. This usually provides abdominal relaxation equal to that produced during spinal anesthesia. This mixture is maintained until the peritoneum is opened, the exploration is made and the abdomen is packed off. No more cyclopropane is added usually, until the hysterectomy is finished and the surgeon is ready for peritoneal closure.

But here is a most important point suggested by Greeley (8). When active respiration reappears it must be amplified usually by passive respiration in order to insure adequate pulmonary ventilation. *Inadequate active respiration with its hypo-ventilation is much more dangerous than passive respiration with hyper-ventilation.*

After the peritoneum is closed or half closed, the breathing bag is emptied and refilled with oxygen or with oxygen and air. This, introduced by passive respiration, immediately reduces the concentration of alveolar cyclopropane by fifty per cent. Another filling of the bag half a minute or a minute later further reduces the pulmonary concentration by fifty per cent. Thus, from two to four such changes during a period of from two to six minutes is sufficient for the re-establishment of active respiration. Once active respiration is fully re-established we stimulate it by the addition of carbon dioxide until maximal pulmonary activity is produced. By means of this procedure we hope to open up all pulmonary alveoli which might have become atelectatic during the anesthesia. When we are satisfied that pulmonary activity has been ample, the soda lime is cut back into the circuit and anesthesia is held at this point until the skin is closed.

Our use of carbon dioxide postoperatively, except in certain cases in which it is contra-indicated or is not needed, consists of the production of a hyperpnea, each half hour for three hours; thereafter, each two hours for twenty-four hours, unless the patient is asleep at night, and thereafter four times daily for from two to five days. This is, of course, varied to some extent to meet varying requirements.

In the matter of elapsed time between reversal of anesthesia and re-establishment of active respiration, the oil-water solubility ratio of cyclopropane becomes the governing factor. During prolonged deep anesthesia in obese individuals the lipoids become heavily laden with cyclopropane. In these cases just after reversal of anesthesia, the diffusion gradient of cyclopropane between fats and lungs is at its greatest. The lungs are almost emptied of cyclopropane after the first three dilutions with oxygen and air. But all cyclopropane that flows

from the fats to the lungs for elimination must pass through blood plasma, and blood plasma can carry but a relatively small quantity of this gas. Therefore, we have a variability in time of re-establishment of active respiration. In our experience, with more than eight thousand anesthesias, there have been four notable cases. In two of these the time was in the neighborhood of twenty minutes, in one forty-four minutes, and in one forty-five minutes. Embarrassing? Yes, but nothing to worry about. The answer is that the tissues in these patients had become so laden with cyclopropane that the blood plasma, with its small carrying capacity, required that much time for transportation of the gas. Ordinarily, after reversal of anesthesia active respiratory effort occurs long before abdominal closure is completed.

Emergence Delirium

Emergence delirium is greater and more active with cyclopropane than with any other anesthetic agent. In sub-anesthetic concentrations this gas is a more potent stimulant to the central nervous system than any other anesthetic agent, and inasmuch as cyclopropane does not depress muscular activity as does ether, this more active delirium upon emergence from anesthesia is to be expected. The delirium seems to be greater in proportion to the depth of anesthesia, although we have had a number of patients with light anesthesia in whom wild delirium was encountered.

We have tried various means of controlling this delirium, such as early and late, heavy and light, and divided preanesthetic medication with opiates and oral barbiturates, none of which had any beneficial effect. In the past two years we have been adding ether during the latter part of the anesthesia with the idea of lessening muscle activity and of slowing the emergence, and this has been our most successful—or shall I say our least unsuccessful—protection against this phenomenon. We may expect delirium in the same sthenic individuals in whom we expect the more severe cardiac arrhythmias, namely, in young, muscular, active adults with a low threshold of nervous irritability.

Signs of Anesthesia

My chart of the signs and stages of anesthesia, published a number of years ago, which my friends have so graciously accepted, will not do for cyclopropane. It is true that if anesthesia is slow enough and light enough, and the anesthetist has an especially keen eye for intercostal muscular depression, this chart might be made to cover cyclopropane anesthesia in some cases. However, cyclopropane anesthesia, as we believe it should be conducted, permits us only three adequate signs as to its depth. These are respiration, color, and the degree of abdominal relaxation.

A word about dilatation of the pupils. For two or three years I have had the growing feeling that this phenomenon is hypoxic in origin, whether the anoxia is gross or histotoxic in character. To state the matter concretely, if we designate the normal pupil as zero and complete eradication of the iris as one hundred per cent., I have never seen, with cyclopropane, more than a twenty-five per cent. dilatation, and this but rarely. Hyperoxygenation, at least from a gross standpoint, is maintained assiduously for all of our patients. Recently I have had reports from three of my former students and associates that, according to this basis of estimation, they have seen pupils dilated to about fifty per cent. in five or ten per cent. of their patients. With ether, although it is possible that pupillary dilatation is of histotoxic origin, it is nevertheless a reliable sign of anesthesia depth. With cyclopropane it is not.

We have found no satisfactory sign with cyclopropane to warn against a too light degree of anesthesia. In the conduct of light anesthesia we can rely upon swallowing or movement of the patient. When swallowing or movement occur we add one or two liters of cyclopropane immediately, and the upward progress of anesthesia is reversed to a satisfactory degree within thirty seconds.

The prediction of approaching shock is the same with cyclopropane as with other anesthetic agents; viz, fall in blood pressure, increase in pulse rate, and slowing of the Arteriolar-Capillary Refill Time. Cyclopropane anesthesia in itself does not produce these.

CONCLUSIONS

Cyclopropane is capable of producing, with safety as we look upon "safety" in anesthesia, abdominal relaxation equal to that produced by the best spinal anesthesia, in all patients. In order to secure this relaxation in sthenic individuals, the apneic technic must be employed. To one who knows respiratory physiology, the apneic technic is safe. Passive respiration is safer than inadequate active respiration. Cardiac arrhythmias occurring during cyclopropane anesthesia, although they must be respected, need not be feared. They are probably reflex in origin and subject to the same influences as other reflexes during anesthesia. They occupy a fairly definite range in cyclopropane anesthesia and anesthesia can be conducted either above or below that range of concentration of cyclopropane. Our experience suggests that ventricular fibrillation and complete heart block are more likely to occur in the arrhythmic range with cyclopropane than either above or below that range. Furthermore, our experience negates the idea that cyclopropane is directly toxic to cardiac muscle as is chloroform. Under cyclopropane, the sthenic patient who is doing his own breathing, is not sufficiently relaxed for abdominal surgery. The asthenic patient may be. Because of the frequency of active emergence de-

lirium in sthenic individuals, ether should be added during the latter part of anesthesia.

Barbiturates administered intravenously immediately before cyclopropane anesthesia protect against cardiac arrhythmias for a period of from thirty minutes to two hours, depending upon the barbiturate employed and the state of sthenicity of the patient.

The signs of anesthesia, as employed with other anesthetic agents, are not practical for cyclopropane. We fear hypoxia during cyclopropane anesthesia.

This report is not contradictory to the many reports that have been made upon cyclopropane. It merely carries the work farther than it has heretofore been carried. May this report not make this technic seem easy. Although it is easy, it must be assiduously studied in all of its phases. The term "Respiratory Paralysis" is a bugaboo. Reversibility to activity of the respiratory neuro-mechanism which has been paralyzed with cyclopropane is as simple as reversibility from depression of any function of the body. In the absence of an irremediable peripheral obstruction, there is no need for death to occur from respiratory paralysis if a competent physician is present when respiratory paralysis occurs.[2]

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[2] Controlled animal and human experiments (not included in this report) in line with these clinical observations have been completed with the cooperation of the following: Clinton Theines and Paul Greeley, Departments of Pharmacology and Physiology, University of Southern California, and Doxie R. Wilson, A. J. Monte, Frederick Proescher, William B. Neff and the Staff of the Santa Clara County Hospital, San Jose, California.

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ABDOMINAL RELAXATION WITH COMBINED REGIONAL AND CYCLOPROPANE ANESTHESIA

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MUCH has been written on the use of cyclopropane as an anesthetic agent, and the conclusions that have been reached have varied widely (1, 2, 3, 4, 5). This paper is based upon my experience in anesthesia for intraabdominal surgical procedures with cyclopropane anesthesia combined with regional anesthetic procedures, sub-arachnoid, peridural and abdominal field blocks.

The surgeon's work is greatly facilitated by adequate abdominal relaxation. This fact is too often neglected by the anesthetist. Administration of cyclopropane in concentrations not greater than necessary to produce apnea does not produce adequate muscle relaxation in all young or robust individuals. Adequate relaxation can be obtained in these types of patients by increasing the concentration of cyclopropane beyond the point of apnea, in which case passive respiration must be maintained by intermittent manual pressure on the breathing bag. This frequently necessitates the use of cyclopropane in concentrations of more than forty per cent.

Our technique of induction differs from that described by Guedel. However it makes little difference how the gas is measured if enough is given. An apparatus with a circle filter and a four liter breathing bag is used. With the face mask snugly applied, approximately two liters of oxygen is admitted to the bag. Cyclopropane is then admitted by measured flow, at the rate of twelve to fifteen hundred cubic centimeters per minute. The point at which apnea appears varies according to the metabolic rate of the patient, the amount of preliminary sedation used, and the pain stimulus that the patient is receiving. Concentrations of cyclopropane sufficient to produce apnea may vary from fifteen to forty per cent. or thereabout in different individuals or in the same individual under different clinical conditions. Preliminary opiates elevate the respiratory threshold. Painful stimuli lower the threshold.

When none of the regional procedures has been used, a flow of cyclopropane of approximately one thousand cubic centimeters per minute is continued beyond the point of apnea until adequate relaxation is obtained, usually from five to eight minutes after the beginning of the anesthesia, passive respiration being maintained by manual pressure on the bag.

The occurrence of cardiac arrhythmias has been one of the points stressed in the use of cyclopropane, and their frequency of occurrence

has mitigated against the use of adequate anesthetic concentrations of the gas. Cardiac arrhythmias ordinarily develop when anesthesia is near the apneic level. We feel that hypo-oxygenation increases the incidence of these arrhythmias. They frequently disappear immediately when the respiratory function is taken over by the anesthetist and adequate pulmonary ventilation with an excess of oxygen is provided. They may re-appear as the concentration of cyclopropane is increased, even in the presence of adequate pulmonary ventilation and oxygenation. Guedel's work has demonstrated that in most instances, when necessary, the anesthesia can be carried below the range of arrhythmias by increasing the concentration of cyclopropane in the anesthetic mixture.

These high concentrations have one notable drawback. Robust individuals between puberty and fifty-five years of age or thereabout, following maintenance of this depth of anesthesia, have a period of active, and sometimes violent, emergence delirium. This delirium is greater when the higher concentrations have been used over a prolonged period. This is one reason that we use a combination of subarachnoid, peridural, or abdominal field block with the administration of cyclopropane. Any of these regional procedures applied alone may be unsatisfactory for surgical procedures within the upper abdomen, due to the incidence of nausea when traction is made upon the abdominal viscera.

Under the necessarily high subarachnoid block for these procedures a paralysis of the intercostal muscles occurs with a resulting decrease of from forty to sixty per cent. in the volume interchange per minute in the lungs. This, combined with the psychic trauma and nausea, sets up an undesirable, vicious cycle. Light cyclopropane anesthesia administered with these blocks, especially the subarachnoid, and peridural, removes the possibility of psychic trauma and permits administration of adequate oxygen to compensate for the depressed respiration.

Our anesthetic technique for upper abdominal procedures has become almost routine (6). The drug used to produce the subarachnoid block depends upon the desired duration of the anesthesia. For operations of one hour or less, procaine in ten per cent. solution is the anesthetic agent of choice. When a longer anesthesia is required, a mixture of procaine and pontocaine, or of pontocaine and glucose is used. The dosage, the volume of the solution, and the anticipated duration of the anesthesia is shown in the accompanying table.

The volume of solution and rate of injection used in this technique eliminates the necessity for depending on gravity to obtain anesthesia at the desired height. In our experience it has given more satisfactory results. The duration of anesthesia has been equal to that obtained with with more concentrated solutions.

Peridural block, after the method of Dogliotti, produces relaxation equal to that of subarachnoid block. However the technique of peri-

SPINAL ANESTHESIA

Anesthesia below umbilicus

Anesthetic		Dose	Site of Inj.	Volume	Rate	Duration
Procaine	10%	100 mg.	L3–L4	3 cc.	3 sec.	45 min.
Procaine	10%	50 mg.	L3–L4	3 cc.	3 sec.	60–75 min.
Pontocaine	1%	5 mg.				
Pontocaine or Nyphanoid	1%	10 mg.	L3–L4	3 cc.	3 sec.	90 min.
Lower Abdominal: Hysterectomy, Appendectomy, etc.						
Procaine	10%	150 mg.	L2–L3	6 cc.	6 sec.	50–60 min.
Procaine	10%	50 mg.	L2–L3	6 cc.	6 sec.	75–90 min.
Pontocaine	1%	10 mg.				
Pontocaine	1%	12 mg.	L2–L3	6 cc.	6 sec.	90–120 min.
Upper Abdominal: Gallbladder, Stomach, etc.						
Procaine	10%	150 mg.	L2–L3	7 cc.	7 sec.	50–60 min.
Procaine	10%	50 mg.	L2–L3	7 cc.	7 sec.	75–90 min.
Pontocaine	1%	10 mg.				
Pontocaine	1%	12 mg.	L2–L3	7 cc.	7 sec.	90–120 min.

dural block requires careful attention to detail in order to avoid the subarachnoid injection of an excessive amount of the anesthetic drug. The fall in blood pressure may be as great as with subarachnoid block, but it is more transient and is accompanied by less respiratory depression. Because of its greater technical difficulties and its slower action, we reserve peridural block for those patients who should have some form of regional block and are prejudiced against spinal anesthesia.

Peridural block is performed by raising a skin wheal over the second or third lumbar interspace. One per cent. procaine is then infiltrated along the course to be taken by the needle used for the spinal puncture. A twenty gauge spinal needle is then inserted until it is engaged within the intraspinous ligament. The stylet is withdrawn and a ten cubic centimeter syringe containing normal saline solution is attached to the needle. As the needle is further advanced, a gentle pressure is exerted on the piston of the syringe. While the needle point is passing through the ligament, it is difficult, due to the density of this structure, to inject any solution. When the needle enters the peridural space, this resistance to the injection disappears. The needle is kept at this position, and after careful aspiration to make certain that the point of the needle is not in the subarachnoid space, ten cubic centimeters of two per cent. procaine solution are injected. Following this injection five minutes are allowed to elapse, the needle remaining in situ during this period. If there is no evidence at this time that the solution has entered the sub-arachnoid space, an additional fifteen or twenty cubic

centimeters of the same solution is injected. Anesthesia will usually be complete in from fifteen to twenty minutes. For upper abdominal procedures with peridural block, the head of the operating table is lowered five or ten degrees while the patient is being prepared. For lower abdominal operations the head of the table is elevated to a like degree.

With those patients who are considered unsafe for subarachnoid or peridural block, an abdominal field block with one-half of one per cent. procaine is used. More cyclopropane is required following the field block than when subarachnoid or peridural block has been employed. Immediately following the administration of the regional block the patient is anesthetized with cyclopropane according to the technique described above. Apnea can easily be produced with a low concentration of cyclopropane by pressure upon the breathing bag synchronous with the inspiratory effort, thus reducing the alveolar concentration of carbon dioxide. In the presence of adequate subarachnoid or peridural block the only advantage of the apneic technique lies in the quieter abdomen that it produces.

SUMMARY

With the combined subarachnoid or peridural blocks and the administration of cyclopropane adequate abdominal relaxation is provided, usually with the cyclopropane anesthesia above the range of cardiac arrhythmias. The slightly deeper cyclopropane anesthesia required with the abdominal field block may carry the patient down into the cardiac arrhythmic range. Emergence delirium is the exception rather than the rule with cyclopropane anesthesia where either of the above mentioned blocks is employed. By reversing anesthesia at the completion of the closure of the peritoneum, many of these patients have regained consciousness by the time they are removed from the surgery. Postoperative pulmonary complications following this procedure occur with about the same frequency as those following straight cyclopropane anesthesia.

COMMENT

The difficulties accompanying subarachnoid, peridural and abdominal field block alone in abdominal surgery are obviated by the adjuvant administration of light cyclopropane anesthesia. This abolishes the element of psychic trauma and of anoxia, which latter circumstance is responsible for many of our difficulties occurring during spinal anesthesia. The combined technique herein described should be considered necessary to good anesthesia in robust subjects and frequently decidedly helpful in other types of patients for abdominal surgery.

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The Nineteenth Annual Congress of Anesthetists will be held in Chicago, Illinois, October 21–25. This date corresponds with the Congress of the American College of Surgeons. The Headquarters, Sessions, Exhibits, and Annual Banquet will be held at the Congress Hotel on Michigan Boulevard. The Congress will consist of Sessions of scientific papers, Anesthesia clinics, and laboratory demonstrations, exhibits of newer anesthetics and apparatus and entertainment for the visiting ladies. Further information may be obtained from Charles J. Wells, M.D., Chairman, Congress Committee on Program and Arrangements, 1932 South Salina Street, Syracuse, New York.

CYCLOPROPANE–AIR–OXYGEN ANESTHESIA

A Preliminary Report *

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The hazard of flammability and explosibility has existed with the use of some inhalation anesthetic drugs ever since their introduction. Ethyl ether presented the greatest potential danger until the last two decades. During this period, there was introduced the two gases: ethylene and cyclopropane, both of which were used with oxygen. Following the introduction of these gases, experiments were performed on the range of explosive concentrations for the several anesthetic drugs combined with air and with oxygen. The results of these experiments have been published. The information derived is of little assistance in preventing accidents when these drugs are used, because the anesthetic concentration of these drugs, when used clinically, is dependent upon the amount required to produce the indicated level of anesthesia. Therefore, they are seldom administered according to a pre-determined percentage. Precautions against static and other electrical potentials have been advocated, in the form of grounding and conditioned atmospheres. There has been no apparent decrease, however, in the number of explosions. Therefore, it was thought worthwhile to undertake an independent and careful study of the flammable and explosive tendencies of the various drugs mentioned above, in combination with one another when they were used with varying percentages of oxygen. If the information so derived would reveal any practical clinical application, the subject consequently could be pursued along these lines.

The Chemistry Department of Purdue University, under the direction of Henry B. Haas, Ph.D., with the sponsorship of the Purdue Research Foundation, has made detailed studies of the exact limits of flammability and explosibility of the commonly employed inhalation anesthetic drugs. Ether, ethylene, and cyclopropane were studied independently when combined with various concentrations of oxygen, as

* Indebtedness is acknowledged to the Purdue Research Foundation and the Department of Chemistry of the Purdue University, whose facilities were made available to us in the pursuit of these investigations.

represented by the pure gas and also in the form of air. These drugs were studied, also, employing mixtures of the gases, nitrous oxide, carbon dioxide, and nitrogen, as diluents. The determinations provided by these experiments, when represented graphically, give the explosive range of the various agents in combination with the diluents, nitrogen, carbon dioxide and nitrous oxide. The complete data on this subject will be published at a later time, illustrated with pertinent graphs of numerous analyses.

Following a study of the graphs, test samples were obtained during various operative procedures on patients, employing different anesthetic combinations. The samples were analyzed and the findings were projected upon graphs to determine the actual flammability of the specific anesthetic mixtures used during clinical anesthesia. We believe that this is the first study made in this manner.

The study of the cyclopropane-nitrogen-oxygen graph for flammability gave scientific proof that there were conditions under which cyclopropane was not explosive. The question remained as to whether anesthesia could be produced safely, and at the same time, provide a non-flammable mixture. The graph (see Fig. 1) represents the range of flammable mixtures of cyclopropane-nitrogen-oxygen; all combinations which are flammable fall within the smaller feathered triangle.

All of the factors, including the analytical estimation which entered into the construction of the graph, were accomplished by careful laboratory research, and therefore, are accurate within the limit of a fraction of one per cent. To apply the graph, take the percentage individually of each component of the combination of nitrogen, cyclopropane, and oxygen, advance from that position on the component's base line to the point where all three lines intersect. If that point of intersection lies within the feathered triangle, then the mixture is flammable and may be explosive. If the point falls outside the feathered triangle, the mixture is both non-flammable and non-explosive. For example: Consider a theoretical mixture of 10 per cent. cyclopropane and 20 per cent. oxygen, the balance being nitrogen. Advance left and inward in a straight line from the proper point on the base line for cyclopropane to a point where that 10 per cent. line will intersect the 20 per cent. line similarly projected upward from the base line for oxygen. Now advance downward to the right from the nitrogen base line to its 70 per cent. line. The point of intersection of the three components will fall within the feathered triangle. The mixture is flammable and explosive.

Observe two facts depicted by the graph. First, irrespective of how great the percentage of oxygen in its mixture with nitrogen, one is always without the explosive range with 2 per cent. or less of cyclopropane. Secondly, one may note from the graph that irrespective of the percentage of cyclopropane in combination with nitrogen, at no time will the mixture be within the explosive range if the oxygen percentage is 11½ per cent. or lower. This latter fact is of greater importance.

No one would be so rash as to predict that we must, perforce, immediately change our technic of anesthetic procedure. Nevertheless, these studies definitely indicate the fact that, in inducing anesthesia with a

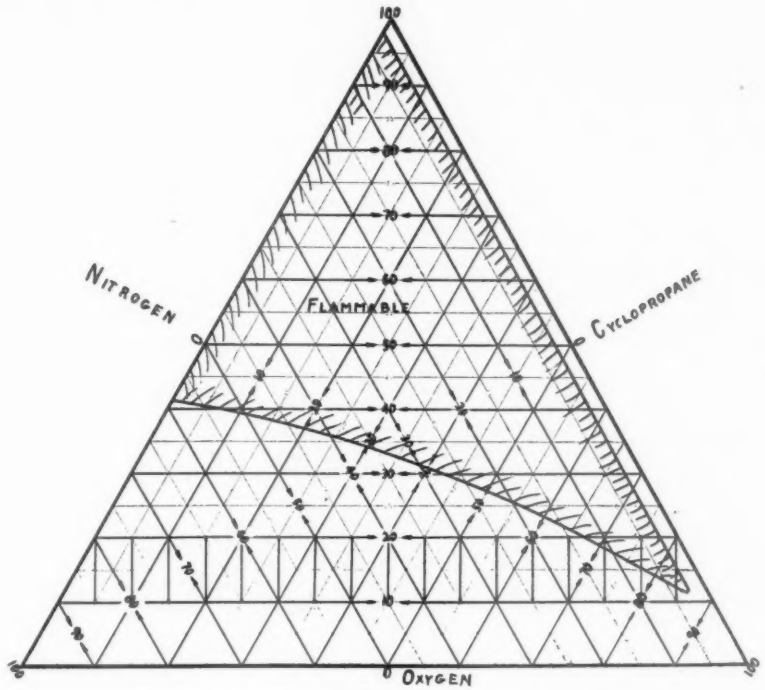

FIG. 1.

breathing bag containing oxygen 100 per cent., and then adding sufficient cyclopropane to establish anesthesia, at once an extremely hazardous explosive range is entered. Also, the practice of flooding or washing out the lungs with pure oxygen at the termination of the surgical procedure gives a similar effect. These two facts can be confirmed indisputably by a study of this graph. If meagre reports coming from centers where explosions have occurred are true, these two periods during anesthesia are the ones during which most of the explosions have occurred. This is what one might expect from the data given in the graph. This research suggests that a reasonable solution of this hazard can be obtained by using inert nitrogen as a diluent both for the induction and for the recovery, thus making it possible for each of these events to occur with reduced percentages of oxygen obtaining. We believe the hazard involved by such management is of less danger comparatively than the risk of flammability.

A further interesting point is shown in that a mixture of 25 per cent.

oxygen, 25 per cent. cyclopropane, and 50 per cent. nitrogen is nonflammable. However, with that percentage of cyclopropane in the mixture, it is quite probable that the patient might become too deeply anesthetized, and respiratory arrest may result. Respiratory arrest occurred with some patients with lesser percentages of cyclopropane, as determined by analyses.

Accordingly, with these facts and data before us, we determined to try cyclopropane-air-oxygen anesthesia. The problem of supplying air is solved in a simple way, as shown in Fig. 2. A bulb is attached to the

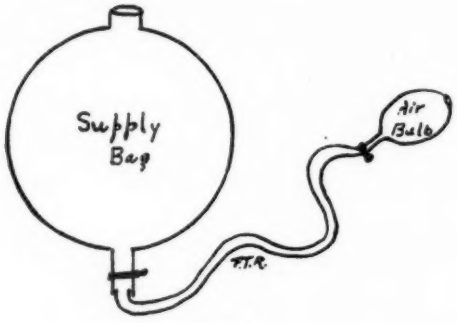

FIG. 2.

bottom of the breathing bag by means of a short length of rubber tubing. The breathing bag is filled first with air by compressions of the bulb. The patient breathes air, while cyclopropane and a metabolic supply of oxygen is added. Meanwhile, the signs of anesthesia are observed closely and constantly. Subsequently, should any of the contents of the bag become lost through leakage or by virtue of a poorly fitting facepiece, air is added by compressing the bulb. Of course, at any time, as it is indicated, air, cyclopropane, or oxygen is added.

A note of sternest warning must be given. To repeat, the physical signs of anesthesia are followed carefully. The signs are similar to those exhibited by other anesthetic agents, resembling more, perhaps, chloroform. The type of respiration and the patient's color, require particular observation, as do the reactions of pupils. It is wise to prognosticate the sequence of affairs by anticipating changes thirty seconds to a minute before they occur. The patient's ears are maintained a slightly pink color. Our analyses show that this can be done, in average cases, with a concentration of oxygen considerably less than 20 per cent. in the mixture. Denarcotization is produced by the addition of air alone. The above method can be used to produce smooth anesthesia and good relaxation.

A discussion of the difference between flammability and explosibility, necessitates a comparison of these terms. Any mixture of gases or vapors which is explosive is flammable also, but not every flammable

mixture of vapors or gases is necessarily explosive, except under certain conditions.

We determined to use a color-index to differentiate clinically between the several degrees of tissue oxygenation. Dusky means slight suboxygenation. Pink (at ear lobes) denotes the normal.

The two cases illustrated will be treated in separate groups of three analyses, for, during each anesthesia, three test samples were obtained.

TABLE 1

Patient 1.
Ruth T. Surgical Procedure—Rectal
Anesthetic—Cyclopropane-Air-Oxygen—Circle Absorber
Sample Source—Supply bag
Stage—III, Plane 1 to 2—⊙
Color—Slightly dusky to pink
Analysis—Cyclopropane 13.8 per cent
Oxygen 15.7 per cent
Nitrogen 70.5 per cent
Carbon Dioxide negligible
Result—Non-flammable

TABLE 2

Patient 1.
Ruth T. Surgical Procedure—Rectal
Anesthetic—Cyclopropane-Air-Oxygen—Circle Absorber
Sample Source—Supply bag
Stage—III, Plane 1 to 2—⊙
Color—Pink
Analysis—Cyclopropane 13.1 per cent
Oxygen 38.0 per cent
Nitrogen 48.9 per cent
Carbon Dioxide negligible
Result—Flammable

TABLE 3

Patient 1.
Ruth T. Surgical Procedure—Rectal
Anesthetic—Cyclopropane-Air-Oxygen—Circle Absorber
Sample Source—Supply bag
Stage—III, Plane 1—←⊙→
Color—Pink
Analysis—Cyclopropane 8.3 per cent
Oxygen 64.9 per cent
Nitrogen 26.8 per cent
Carbon Dioxide negligible
Result—Flammable

The first patient was a white female scheduled for a rectal procedure. We determined, before-hand, to start this patient on air only, induce and maintain the anesthesia with cyclopropane, then gradually add oxygen to produce extreme pinkness of the lobes of the ears. We wanted to ascertain the percentages of the gases and the degree of flammability. The breathing bag was filled with air, and the mask was applied to the face. A small flow of cyclopropane was started. All signs of anesthesia were watched carefully. The depth of anes-

thesia soon reached stage III, plane 2, with 200 cc. of oxygen flowing. Color—slightly dusky to pink; i.e., the patient was slightly suboxygenated. Then a sample (Table 1) was obtained from the breathing bag. The analysis demonstrated the mixture to be non-flammable, and safe as far as explosibility is concerned. Then air and plus oxygen were added to the mixture. The plane of anesthesia then changed to stage III, plane 1. The analysis is shown (Table 2). This concentration of cyclopropane is not only flammable but is definitely explosive. Further oxygen was added and the depth of anesthesia was allowed to become lighter. Sample three (Table 3) was taken, and the analysis is shown. This mixture is very dangerously explosive. This analysis parallels the many tests made during the ordinary cyclopropane-oxygen anesthesias previously taken.

The results obtained in Patient 1, encouraged further investigation. For the next patient, we determined to maintain a sufficiently low concentration of oxygen to stay outside the explosive limits throughout the anesthesia.

TABLE 4

Patient 2
Robert K. (Hawaiian) Surgical Procedure—Rectal
Anesthetic—Cyclopropane-Air-Oxygen—Circle Absorber
Sample Source—Supply bag
Stage—III, Plane 2—←⊙→
Color—Dusky

Analysis—Cyclopropane	15.5 per cent
Oxygen	6.1 per cent
Nitrogen	78.4 per cent
Carbon Dioxide	negligible

Result—Non-flammable
Respiratory arrest resulted.

TABLE 5

Patient 2
Robert K. (Hawaiian) Surgical Procedure—Rectal
Anesthetic—Cyclopropane-Air-Oxygen—Circle Absorber
Sample Source—Supply bag
Stage—III, Plane 1—←⊙→
Color—Pink

Analysis—Cyclopropane	10.6 per cent
Oxygen	7.0 per cent
Nitrogen	82.4 per cent
Carbon Dioxide	negligible

Result—Non-flammable

TABLE 6

Patient 2
Robert K. (Hawaiian) Surgical Procedure—Rectal
Anesthetic—Cyclopropane-Air-Oxygen—Circle Absorber
Sample Source—Supply bag
Stage—III, Plane 1—
Color—Pink

Analysis—Cyclopropane	9.5 per cent
Oxygen	6.0 per cent
Nitrogen	84.5 per cent
Carbon Dioxide	negligible

Result—Non-flammable
Awale in 3 minutes.

A young, vigorous Hawaiian, which characteristics constitute both an advantage and a disadvantage, was chosen. It was a disadvantage in that the color-index was more difficult to read; it was an advantage in that, if successful, it would be a severe test of the method. As soon as the anesthesia was levelled off at stage III, plane 2, the first sample was taken. The color was slightly dusky (Table 4). This mixture is non-flammable and non-explosive. With this percentage of cyclopropane, respiratory arrest was produced. As is well known, this is neither an unusual nor an embarrassing situation. With the mask off the face and by means of artificial respiration by simple pressure on the chest, the respiration was resumed and the anesthesia decreased to stage III, plane 1. In Table 5, the analysis of the second sample, then taken, is shown. Note that the color is normal. This sample, too, is non-flammable and non-explosive.

The anesthesia was maintained at this level for the remaining ten minutes of the operation. Toward the close, after no more air or cyclopropane had been added to the breathing bag, and only the required amount of oxygen had been flowing, the final sample was taken. The color was normal. The analysis (Table 6) was the same, essentially, as the one previously taken and was non-flammable and non-explosive. The patient was awake and thoroughly oriented mentally within three minutes. No nausea or vomiting was exhibited. We believe this is the first recorded case of cyclopropane anesthesia, during which an absolutely non-flammable mixture of cyclopropane was employed, as determined by analyses, throughout the entire procedure.

Upon examining the three analyses of patient 2 and plotting them upon the graph, it is interesting to observe that in the first sample, it would have been possible to have carried an oxygen percentage of 22 per cent., in the second an oxygen percentage of 18 per cent., and in the third an oxygen percentage of 17 per cent. and still have remained outside the explosive and flammable limits. These percentages of oxygen, in this particular patient, would have been ample to have carried him with a definitely pink-plus color-index.

No one knows at any one particular moment for any one particular patient exactly what the percentages contained in mixture are, except by rough approximation. It would not require a great deal of modification of existing instruments to provide equipment on present-day machines to serve as a device upon which constant readings of "danger" and "safe" would be indicated with regard to explosibility. Similar equipment is in use in the mining industry.

Final comment: In all the samples during which we used the closed circle, carbon dioxide absorption technic of anesthesia, not in a single instance did we find more than a mere trace of carbon dioxide. A fresh or relatively new supply of soda-lime was employed in the canister for each patient. This speaks well for the method.

In making this data at once available in a preliminary report, it is

likely the results may arouse the interest of anesthetists. For generations, ether and chloroform have been administered with air. Why not employ cyclopropane with air? It seems reasonable and is based on sound physiologic principles. In fact, apart from the waste, in order to get sufficient oxygen, straight cyclopropane-air anesthesia with a partially open system should be feasible.

Normally, we breathe 80 per cent. nitrogen and 20 per cent. oxygen. Our physiological requirements are adjusted to these concentrations. The value of excess oxygen, under reasonably normal conditions, might be disputed, except in the presence of respiratory obstruction or definitely anoxic states. Authorities aver that, in normal concentrations of nitrogen and oxygen in the air and under ordinary atmospheric pressures, the blood stream is 98 per cent. saturated and that increasing the percentage of oxygen does not correspondingly increase this saturation. The residual air in the lung normally contains 13 to 14 per cent. oxygen plus 5.5 per cent. carbon dioxide when the individual is breathing air. Individuals ascending 6,000 to 8,000 feet above sea level in airplanes, or those living constantly at such altitudes are fairly comfortable in these atmospheres in spite of the reduced partial pressure of oxygen which is equivalent to reducing the oxygen percentage at sea level. In semi-closed, nitrous oxide-oxygen anesthesia little thought was given toward maintaining anesthesia with these patients definitely suboxygenated for protracted periods of time. We neither dare nor care to decry the obvious benefits of plentiful supplies of oxygen available to the tissues. We may be required, however, to change certain of our ideas because of the hazard of explosion.

We are happy to present the idea of cyclopropane-air-oxygen anesthesia because it appeals to us as an original and rational approach to a difficult problem. We are hopeful that anesthetists will experiment with it. Since the initial studies, it has been employed for major surgical procedures including thoracoplasty, during which the radio-knife was employed. The method is not fool-proof. It is neither a panacea nor a cure-all for hazards of flammability, nor is it offered as such. We make no claims of dogmatic absolutism. We merely suggest its clinical use as a possible application of the experiments conducted concerning the flammability of cyclopropane.

Conclusions

Excepting in nitrous oxide-oxygen anesthesia, without the addition of ether, ethylene, cyclopropane, or some like agents, the hazards of flammability and explosion are present in using the ordinary inhalation anesthetic agents under uncontrolled conditions. The only real solution for inhalation anesthesia would be the development of a nonflammable and non-explosive gas or volatile liquid possessing the required anesthetic properties. Research toward this end is being projected.

A method of administration of cyclopropane-air-oxygen anesthesia is described. Certain changes in technic which will tend to minimize or even abolish the hazard of explosion are suggested.

We believe it possible to develop an indicating device to attach to present-day anesthetic apparatus which would show instantly and perhaps constantly whether or not the mixture in use falls into or with the range of explosibility.

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The Board of Directors of the American Society of Regional Anesthesia, Inc., announce that a sum of money has been set aside to provide "The Labat Research Fellowship" in memory of Gaston Labat, M.D., founder of the society. The funds will be awarded to an anesthetist or surgeon for aid in pursuing original laboratory investigations in regional anesthesia. Inquiries and applications should be made to H. M. Wertheim, M.D., 1088 Park Avenue, New York, N. Y.

THE ROLE OF THE LIVER AND THE KIDNEYS FROM THE STANDPOINT OF THE ANESTHETIST [1]

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THE liver and the kidneys play a very important role in anesthesia from the standpoints of both the anesthetist and the surgeon. In health the normally functioning liver and kidneys may tolerate strains necessitated by the maintenance of anesthesia, but when the functions of these organs have been impaired by disease, hereditary disturbances, or by chemical poisonings or by diet, they may very easily be further damaged to the extent that recovery of the patient will be delayed, or death may result. In discussing a subject of this nature it is necessary to rely largely on the results of investigative work which has been carried out experimentally. Some of the results which have been obtained by various investigators have been confirmed clinically. However, clinical results are sometimes misleading, for usually we have the complicating factor of a surgical procedure's being carried out on the patient during anesthesia. The factors of trauma to tissues and shock undoubtedly change the picture in a great many instances. We shall review the literature rather briefly and try to draw some conclusions from the results of reported investigations.

EFFECTS OF ANESTHESIA ON THE LIVER

For many years laboratory workers have warned us of the dangers of anesthesia produced by chloroform. In spite of these warnings, however, chloroform still enjoys a prominent place in anesthesia, particularly in Europe. Many anesthetists and surgeons alike seem to be of the opinion that damage follows the use of chloroform only in the exceptional or badly managed patient. "This is not correct. It has rightly been said that chloroform anesthesia is synonymous with chloroform poisoning" (2). In 1909 Whipple and Sperry concluded, on the basis of their work on chloroform poisoning, that chloroform anesthesia carried out for any considerable length of time invariably produces central necrosis of the liver. They found that there was a variance in susceptibility from animal to animal and from man to man. A short period of chloroform anesthesia may prove fatal or may produce very little hepatic damage. Whipple and Sperry mentioned one case in which chloroform anesthesia of only thirty-five minutes' duration pro-

[1] Read before the meeting of the New England Society of Anesthetists, Boston, Massachusetts, February 26, 1940.

duced almost complete necrosis of the liver and death in man. Chloroform anesthesia of a half hour in duration usually will produce fatty changes in the liver, which are demonstrable only after a lapse of six to ten hours. The maximal damage is demonstrable in about forty-eight hours. Dogs which have been fasted for twenty-four hours and then anesthetized with chloroform for one and a half hours suffer from central necrosis of the hepatic lobules which involve a third to a half the area of the lobules. Repair of this damage requires seven to twelve days.

MacNider (24) in 1935 confirmed the work of Whipple and Sperry and also found that when hepatic function is tested with phenoltetrachlorphthalein, an increase in the initial concentration of the dye in the plasma occurs. If, however, epithelial repair occurs with production of a normal type of hepatic cell, the dye values return to normal. In some animals a normal type of hepatic cell does not develop to replace the normal tissue but instead, flattened cord-like epithelium develops. This new structure may or may not function normally as measured by the dye test. The damage of the hepatic lobule is central. Fat appears first in the intermediate region, then extends toward the periphery; the entire lobule may become intensely fatty (16). Vacuoles appear, swelling and necrosis of the cells become evident, and fatty degeneration occurs. The early changes take place usually around the central veins. In dogs which have been fasted for four days, anesthesia for one hour with chloroform usually will produce severe central necrosis often extending over a half to two-thirds of each lobule. Some of the animals may die within three or four days. The livers of these animals show approximately four-fifths of the liver to be in a necrotic condition (8). It is noted that the effect on fasting animals is greater than the effect on normal animals.

In dogs suffering from chloroform poisoning, the secretion of phenoltetrachlorphthalein is decreased; the amount of fibrinogen is decreased; the galactose and levulose tolerance is decreased; lipase is increased and some disturbance occurs in the nitrogen partition in the urine. In dogs which receive a fatal dose of chloroform, a marked decrease of urea nitrogen is found, without an accompanying increase in free amino acids or ammonia nitrogen. The increase in nonprotein nitrogen and urea and amino-nitrogen in the blood is associated with an increase of the same substances in the urine; therefore, it would appear that there are an increased protein catabolism and a renal insufficiency causing accumulation (25).

The concentration of fibrinogen decreases in severe chloroform poisoning. The blood fibrinogen value is a good index of hepatic damage. Icterus is always present when severe necrosis caused by chloroform has taken place. The urea-forming capacity is lost only in the presence of an extremely severe or fatal liver injury. The uric acid mechanism is disturbed by a lesser degree of damage (8). Ec-

chymosis and hemorrhages often occur in the peritoneum and upper portion of the gastro-intestinal tract. Some degree of fat necrosis and ecchymosis is found in the pancreas. Often, some degree of fatty degeneration is found in the kidney and heart of animals following chloroform necrosis (43). Chloroform poisoning may cause severe hepatic necrosis and placental necrosis with separation and hemorrhage in pregnant animals. This serves as potent evidence that the theory of resistance to chloroform during pregnancy is without foundation (43). Pregnant dogs are as susceptible to chloroform poisoning, both before delivery and during labor, as are normal dogs, although no damage is found in the liver or other organs of the fetus (41). Graham in 1915 brought forth evidence that pups were resistant to chloroform poisoning because of protection afforded by a high concentration of glycogen in the liver. He found that anesthesia of two hours' duration produced no effect on the liver of these animals. An equal period of anesthesia in the adult dog caused marked hepatic necrosis and often death. Graham found that if the young animals were fasted or rendered diabetic, hepatic necrosis could be readily produced. Anderson in 1932 found that an anesthetic mixture of 1 part alcohol, 2 parts chloroform and 3 parts ether, which contains only two-sevenths as much chloroform as is used in straight chloroform anesthesia, produced hepatic necrosis in white rats identical to that produced by chloroform anesthesia alone. He found that newly formed hepatic cells were more resistant than old cells in non-fasting animals.

Rosenthal and Bourne, using the bromsulfalein test, found that brief periods of anesthesia produced by chloroform result in both immediate and delayed toxic effects on the liver. The effects of ether were transitory; recovery was complete within twenty-four hours. Nitrous oxide and ethylene did not cause changes in elimination of the dye from the liver so long as anoxemia was not present. However, in the presence of anoxemia, both immediate and delayed effects on the liver were noted. Cyanosis itself increased the toxic effect of the anesthetic agent on the liver. Rosenthal and Bourne believed that ethylene is the safest anesthetic agent to use in the presence of hepatic injury.

Bollman in 1929 stated, "In the selection of agents for use as anesthetics a primary consideration has been that these substances should not produce permanent or irreparable injury to any organ or tissue when administered in amounts sufficient to produce anesthesia." He stated that the response of the liver to the various anesthetics depends on two factors; namely, the agent administered and the condition of the liver. The glycogen content of the liver is almost always lowered in the presence of hepatic disease. It is also lowered in nutritional disturbances which do not necessarily involve the liver. Goldschmidt, Ravdin and Lucké (10) have found that the use of oxygen as a volatilizing agent for chloroform gives approximately the same degree of pro-

tection against hepatic necrosis as does a high carbohydrate diet. Ravdin, Vars, Goldschmidt and Klingensmith (33) found that in normal dogs anesthetized with chloroform the value for sugar in the blood was approximately the same whether air or oxygen was used as the volatilizing agent. Anoxemia occurring during anesthesia produced a great increase in the values for sugar in the blood. Prolonged hyperglycemia followed the cessation of anesthesia, probably as a result of the effect of chloroform on the hepatic cells. The concentration of glycogen in the liver was steadily reduced during anesthesia, with a loss of approximately 35 per cent. during that period. Glycogen in the liver continued to disappear after anesthesia until at the end of twenty-four hours, 94 per cent. of the glycogen in the liver had been lost. Ravdin and associates also found that volatilization of the chloroform with oxygen leads to a more rapid restoration of glycogen in the liver. As the concentration of glycogen decreased, the concentration of fatty acids in the liver increased. Ether lowers the content of glycogen in the liver of cats about 15 to 20 per cent. during the first five or six minutes of anesthesia. As anesthesia proceeds, the glycogen continues to decrease until, after a half hour of anesthesia, somewhat less than half the original content of glycogen in the liver remains (9). Anesthesia produced with chloroform in cats reduces the content of glycogen in the liver to about a fourth its initial value at the end of fifty minutes of anesthesia. During this time the sugar content of the blood increases about 200 per cent. (27). Ether produces a slight impairment of hepatic function in dogs as can be shown by the bromsulfalein test. This effect disappears the following day (36). A two-hour anesthesia produced by ether in a dog is followed by a temporary decrease in the hepatic secretion and elimination of dye during the twenty-four hours following anesthesia. The injury is not great enough to be ascertained histologically (42). Many theories have been evolved to explain the hyperglycemia caused by ether which occurs in normal animals with a normal content of glycogen in the liver. Indirect action of the anesthetic agent upon the liver, indirect action through the general stimulation associated with the excitement stage of anesthesia, asphyxia or spastic congestion, accompaniments of anesthetic changes in the hydrogen-ion concentration of the blood and the reflex secretion of epinephrine are some of the explanations that have been advanced.

Neither ethylene nor nitrous oxide anesthesia produces any impairment of hepatic function or pigment metabolism in dogs, provided that the animal is well oxygenated. If anoxemia accompanies the administration of either of these anesthetic agents, both immediate and delayed toxic effects can be demonstrated by the method of excretion of dye (36).

Anesthesia produced by divinyl ether may result in hepatic necrosis in the dog. Histologically, the picture of central lobar necrosis re-

sembling that produced by chloroform anesthesia can be produced with divinyl ether, although the degree is usually less marked. The duration of anesthesia produced by divinyl ether seems to be a definite factor in the production of hepatic necrosis, the hazard increasing as the duration of anesthesia increases (11). Ravdin and associates (35), reporting the results obtained in 3,407 instances of anesthesia produced with vinyl ether, stated that they have found no evidence that the agent is contraindicated in renal or cardiac disease. They used the agent many times in the presence of disease without indication of deleterious effects. In 1937 Goldschmidt, Ravdin and Lucké (10) showed that when chloroform and divinyl ether are employed for anesthesia in dogs, less hepatic damage occurs when the two agents are administered with oxygen than when they are administered with air. The protective action of oxygen in combating hepatic necrosis following the administration of chloroform was approximately equivalent to that afforded by previous ingestion of a diet high in carbohydrates. Oxygen is about equally effective in preventing hepatic damage from chloroform and from divinyl ether. A high glycogen content of the liver preceding anesthesia produced by divinyl ether affords greater protection to the liver than does an excess of oxygen. This protection is greater against damage from divinyl ether than from chloroform in dogs. A deficient content of oxygen in the inspired air may result in hepatic damage.

Anesthesia produced by cyclopropane does not impair hepatic function in the normal dog even after repeated or prolonged administration of this agent. It does not increase hepatic damage previously produced by chloroform nor does it impede the usual recovery of the liver from chloroform poisoning. It apparently does not produce hepatic impairment in starving dogs even after prolonged anesthesia (31). It has been previously stated that anoxemia alone will produce hepatic damage in normal animals. Perhaps the absence of hepatic damage following anesthesia produced by cyclopropane in starving animals can be explained by the protection afforded by the high concentration of oxygen which is administered with the agent. Raginsky and Bourne reported the results of their findings in thirty-four obstetrical cases in which thirty-three patients were normal and in which one had eclampsia. Practically no dye was retained twenty-four hours after anesthesia in the blood of the normal patients. The pre-existing damage was not increased in the liver of the eclamptic patient.

Bruger, Bourne and Dreyer reported on the results obtained from experimental work in dogs under anesthesia produced by tribromethanol. They found that after twenty-four hours, three of the eleven dogs showed retention of dye greater than 10 per cent. These three animals showed a retention of 30 per cent., 15 per cent. and 25 per cent., respectively, twenty-four hours after anesthesia, but in every instance the retention was transient; no delayed damage was found. Two observa-

tions in man showed no retention of dye twenty-four hours after the administration of 100 mg. of tribromethanol per kilogram of body weight. Bourne and Raginsky (4) in 1931 found that when tribromethanol was repeatedly administered to dogs, it produced only mild parenchymatous degeneration of the liver and kidneys. Occasionally, slight fatty degeneration occurred in the liver. In a liver experimentally damaged by chloroform, tribromethanol caused 5 to 30 per cent. additional decrease in function as shown by the bromsulfalein test. This decrease seemed to be proportional to the severity of the original damage. It was said not to affect the total period of recovery from chloroform poisoning. In 1930 Bourne, Bruger and Dreyer (6) administered sodium amytal to dogs in doses of 40 to 60 mg. per kilogram of body weight. Twenty-four hours after the administration of this drug the hepatic function as tested with bromsulfalein showed retention of as much as 20 per cent. of the dye. This retention was transient. No evidence was found of delayed hepatic damage. In three human beings no retention of dye was found twenty-four hours after anesthesia produced with 1,000 mg. of sodium amytal. Sollman stated that changes in hepatic function produced by toxic doses of barbiturates resembled those caused by infectious diseases.

Pratt in 1933, working with normal rabbits and rabbits with hepatic damage produced by phosphorus and carbon tetrachloride, found that in those animals who had hepatic damage severe enough to delay the removal of the dye, a prolonged period of depression was produced by pentobarbital. The duration of the action of barbital does not seem to be affected by the excretory function of the liver. She attributed the long action of the barbital to a stability which apparently avoids destruction within the liver and allows most of the drug to be excreted by the kidneys. In 1937 Ravdin (34) and associates reported the data concerning 2,675 anesthetizations with divinyl ether. In this series of anesthetizations they observed no instance of hepatic damage, although damage was guarded against by the prevention of anoxemia and by limitation of the length of anesthesia to about one hour. Ravdin and associates (34) stated that anesthesia produced by chloroform would produce necrosis of the liver in the dog following one hour of anesthesia, but that it required three hours of anesthesia with divinyl ether to produce necrosis of the liver in this animal and that even then, the hepatic damage was not great.

Ravdin (32), writing alone in 1937, said: "The choice of the proper anesthetic for patients with hepatic insufficiency is of the greatest importance. It has been well established for many years that chloroform should not be used in these patients. We have good evidence that ether also can cause severe damage in the presence of anoxemia. Because of the slowing of the vascular stream in ductal obstruction, there is local anoxemia of the liver tissue. Some of the violent postoperative reactions after the use of ether are without doubt due to the damage of the liver cells."

An understanding of normal hepatic function and a knowledge of the condition of the patient's liver must be present if the physician is to evaluate the relationship of such function and condition to anesthesia. Agents which may be well tolerated by the normal liver may cause severe damage to the diseased organ or to the organ which has been depleted of its glycogen. For example, the liver is less likely to show evidence of damage following the administration of hepatic poisoning if the content of glycogen in the liver is within normal limits. The regulation of the blood sugar is one of the chief functions of the liver. The administration of most of the commonly used anesthetic agents to normal animals causes an increase in blood sugar. This increase often does not occur if the value for glycogen has been depleted by fasting. Bollman in 1929 considered that the increase in blood sugar during anesthesia offered some evidence of the state of hepatic function and pointed out that when the expected increase of sugar in the blood does not occur, hepatic degeneration frequently follows (2). This fact should be borne in mind for anesthetists sometimes administer anesthetic agents to diabetic patients merely because it is known that a particular agent has very little effect on the blood sugar. It is entirely possible that the administration of an agent, such as the shorter-acting barbiturates, to a diabetic patient who has some degree of acidosis and whose liver is depleted of glycogen, may cause severe damage to the liver, for it is generally believed that the liver performs the important action of detoxifying most of the shorter-acting barbiturates.

Effects of Anesthesia on the Kidneys

Beecher stated, "The close relationship of urine formation and the circulation of the blood through the kidneys is a matter of common knowledge. Salient points of this relationship are as follows. Increase in both general arterial pressure and renal blood flow results in an increase in urine formation. A marked fall in blood pressure may greatly diminish urine secretion, and in some cases stop it altogether. Asphyxia or intravenous injection of epinephrine produces an elevated blood pressure, but also constricts the renal blood vessels. This results in a diminished blood flow through the kidneys and in decreased urine formation. Anoxia quickly damages the 'colloidal membrane' of the kidneys, the glomerular epithelium, and allows it to become permeable to protein, albumin and blood. Thus urine which is abnormal in character is formed. Constriction of the renal vein results in an elevated glomerular pressure, and the blood flow through the kidney is accordingly greatly reduced. This also will produce a damaging anoxia. Fused masses of red blood cells block the glomeruli and check their function. Engorged renal veins compress the collecting tubules, and the flow of urine is interrupted. This type of interference may be produced by cardiac decompensation. Anesthesia may initiate

these effects through its action on the circulation. In addition, certain anesthetics, notably chloroform, produce severe direct kidney damage. It is not surprising, then, that disturbances of kidney function occur during and following anesthesia'' (2). In 1905 Pringle and associates observed the effects of anesthesia produced by ether and operation on the urinary output and nitrogen content of patients. They found that the excretion of urine and nitrogen was slightly stimulated during ether induction, but that excretion rapidly decreased until it became almost nil during the third half hour of anesthesia. The urinary excretion was only about one-third of normal during the twenty-four hour period following anesthesia. Miller and Cabot reported on the renal function of patients during anesthesia produced by ether and operation. They found that the output of the kidneys was decreased 18.8 per cent. in 335 patients. Normal excretion was re-established in twenty-four to forty-eight hours. If morphine and atropine are given to dogs a half hour before induction of anesthesia with ether, the renal function is not inhibited to the extent that it is in animals receiving no premedication. Etherized animals who have undergone unilateral sympathectomy excrete indigo carmine as well from the sympathectomized kidney as normally. While the excretion from the normal kidney is suppressed, thus ether probably causes a reflex effect on the renal vessels (13).

It is believed by many physicians that spinal anesthesia will overcome suppressed renal function in many instances. In these cases it is presumed that the arterioles and capillaries of the kidney are contracted and that the blood flow is at a minimum. Spinal anesthesia blocks the sympathetic nerves and results in a dilatation of the vessels. The blood flow in increased and urinary excretion is resumed (2). In 1920 MacNider (20) found that forty-three out of 131 normal dogs anesthetized with ether would suffer from anuria for either a short time or permanently. When anuria occurred, it appeared one to two hours after the establishment of anesthesia or it was associated with a marked decrease in the blood pressure. In the anuria associated with lowered blood pressure, the flow of urine was re-established following the administration of normal sodium chloride solution or 1 per cent. solution of thiobromine.

MacNider carried out more studies on renal function in dogs anesthetized with ether. He found a great difference in renal function under ether anesthesia in old dogs and in young dogs. In young animals and adult animals up to two or three years of age, no marked reduction in formation of urine was shown during anesthesia. Renal function as determined by dye tests showed very little change from the normal. The urine contained no albumin or casts. The alkali reserve in the blood remained stable throughout anesthesia. Animals from four to eleven years of age showed a marked reduction in the formation of urine or suffered from anuria after one hour of ether anesthesia. The dye test showed a reduction of renal function. Al-

bumin and casts were found in the urine; the alkali reserve of the blood was reduced. The changes in the blood, particularly the decrease in the alkali reserve, were responsible for the renal failure in the older animals. It was found that the kidneys of the older dogs contained more stainable lipoid material in the renal epithelium and in the glomerular capillaries than did the kidneys of the younger animals. Because the older group of animals had shown a decrease in the alkali reserve, a dilute solution of either sodium bicarbonate or glucose was administered intravenously before ether was administered. Material obtained for biopsy showed that the alkaline solution, and to a lesser extent glucose, modified or diminished the amount of stainable lipoid material (21). It was found that two hours of anesthesia produced by ether could be carried out without materially diminishing renal function. Renal epithelial necrosis and endothelial necrosis were not found. When sodium bicarbonate or glucose was administered, the lipoid material of the kidney was altered or removed. The senile kidney then became comparable to the kidney of a young animal and withstood anesthesia with ether without degeneration (22).

The increased susceptibility of pregnant animals to ether has been demonstrated to be referable to a similar increase of lipoid material within the renal epithelium (2). Animals which have temporary anuria during anesthesia with ether but later respond to diuretic solutions show practically no degenerative changes in the kidney. The glomeruli appear normal but cloudy swelling is present in the epithelium of the convoluted tubules. However, these cells are without vacuolation or necrosis. There is an accumulation of fat in the ascending limb of Henle's loop and there is no loss of alkali reserve in these animals. Restoration of blood pressure brings about excretion of urine. The primary injection of a solution of glucose in pregnant dogs before anesthesia with ether is produced is more effective in maintaining an acid-base balance in young animals. In older animals, when adequate protection is not produced, a reduction of the alkali reserve takes place and urinary output is decreased. Albumin casts and diacetic acid are found in the urine (23).

MacNider in 1920 (20), 1929 (23), and 1935 (24), found that during anesthesia produced by chloroform, dogs had anuria by the time the induction was complete. The alkali reserve became rapidly depleted. In these animals the use of diuretic solutions failed to induce urinary flow. In two-hour anesthesia produced by chloroform in dogs a preliminary injection of glucose failed to give a protective action. In a series of dogs in which acute nephritis had been produced by administering uranium nitrate, the animals were anesthetized with a solution of alcohol and chloroform. These animals were afflicted by anuria very quickly after anesthesia had been established and they did not respond to the use of diuretics. It was shown that the anuria was not caused by a lowering of systolic blood pressure or by an inability of the

diuretics to cause dilatation of the renal vessels, but that it was caused by the action of the anesthetic agents in producing edema and necrosis of the tubular epithelium. In kidneys of dogs which had undergone prolonged anesthesia with chloroform, the glomeruli appeared normal. Severe swelling and edema were present in the convoluted tubules. Vacuolation and necrosis were present; fat was present in both the epithelium and convoluted tubules and epithelium of Henle's loop. Hemorrhages occasionally were found in the kidneys.

The changes found in the kidneys of dogs and man following anesthesia produced by chloroform are comparable. Daft and associates in 1936 found in studies on dogs following one hour of anesthesia with chloroform that a great increase in nitrogen in the urine takes place during the first four days following anesthesia. Part of the excess nitrogen can be accounted for by the necrosis in the liver. It is believed that toxic-split products escape from the dead hepatic cells and cause damage to tissue elsewhere in the body. Hawk in 1908 stated that the excretion of nitrogen in man under anesthesia with chloroform is increased in all its forms with only one exception. Urea, creatinine, uric acid and ammonia are all increased. Hippuric acid is decreased. Bourne and Stehle (5) stated that in man under anesthesia produced by chloroform there is a decrease in the excretion of phosphorus of about 50 per cent. of normal. Luckhardt and Lewis found that in dogs anesthetized for three hours with ethylene there was no alteration in the excretion of dye from the kidney. The elimination of Ringer's solution following intravenous injection was normal. Albuminuria and glycosuria were not found. Waters and Schmidt (40) found that during anesthesia produced by cyclopropane the urinary output is suppressed sometimes to a state of anuria. There is a compensatory increase some hours later. Veal and associates have shown in normal rabbits that rather a large margin of safety exists between the anesthetic dose and the lethal dose of tribromethanol. If a mild degree of nephritis is present, the margin of safety does not exist. Death seems to be the result of failure of the kidneys to excrete tribromethanol glycuronate.

Bruger and associates found that in dogs deeply anesthetized with tribromethanol, anuria developed almost immediately. After fifteen to thirty minutes of anuria, oliguria developed. Some observations in man substantiate these findings. Pitt reported the effects of anesthesia with tribromethanol for operations on a group of patients. He found that the concentration of urea in the blood increased 2.6 per cent. in a group of five patients less than fifteen years of age, 3.6 per cent. in a group of sixteen patients less than twenty-five years of age, 4.1 per cent. in a group of eight patients less than thirty-five years of age, and 5.8 per cent. in a group of four patients less than forty-five years of age. His work showed that the increase in urea in the blood was greater in groups of older patients and that it was greatly increased in

patients who had a diminished concentrating power of the kidneys. Bruger and associates found that under anesthesia produced by tribromethanol the phosphoric acid output in dogs is increased. The maximum is reached from six to twenty-four hours following administration of the anesthetic agent. Hirschfelder and Haury concluded from their studies on nephrectomized rabbits that barbital and phenobarbital probably are excreted from the kidneys in an unchanged form. Most of the remaining shorter-acting barbiturates are probably detoxified in the liver.

Beecher stated that the urinary output in dogs receiving small nonsedative doses of sodium phenobarbital ingested with 200 cc. of water was diminished to about a third of the urinary output of the control animals. Johnson and associates, studying dogs when the animals were under the influence of anesthesia produced by soluble barbital, found that the recovery time was reduced more than half when the anesthesia was followed by intravenous administration of 1 liter of a solution of 10 per cent. dextrose.

PRACTICAL CONSIDERATIONS AND SAFEGUARDS

Diabetic Patients.—Tovell and Betlach made blood sugar determinations before and after production of anesthesia with pentothal sodium in diabetic patients whose diabetes was well controlled. They found that the increase in blood sugar following anesthesia and operation was insignificant. However, we feel that additional work should be done with pentothal anesthesia in diabetic patients before the agent becomes commonly accepted as one of the safer agents to use for this type of patient.

Patients Who Have Hepatic Disease.—The barbiturates, with the possible exception of barbital and phenobarbital, should be administered with extreme caution to patients suffering from any hepatic disease. A case recently came to our attention in which pentothal sodium was used for the anesthetic agent in peritoneoscopy. A very small amount of the drug was administered for induction of the anesthesia. Following the induction very little more of the drug was required. The patient was found to have marked cirrhosis of the liver. This patient slept for about twenty-four hours. An ordinary healthy individual should have recovered from a comparable amount of the anesthetic agent in ten minutes' time.

Patients Suffering from Chloroform Poisoning.—In patients suffering from chloroform poisoning, the use of dextrose, and insulin when necessary, might be of advantage in helping to restore normal hepatic function, although this suggestion has never been proved definitely. Dextrose and insulin administered preoperatively probably would be of advantage for patients in an acute toxic state who occasionally come to surgery. Such people usually are found to be suffering from some degree of acidosis and the store of glycogen in the liver has become

depleted. We feel that if this routine were carried out for this type of patient the postoperative morbidity would be materially lessened. It has been repeatedly pointed out in various experimental studies that glucose administered intravenously before anesthesia affords the liver a great deal of protection from the various anesthetic drugs. Changes in the liver following the administration of chloroform, ether, divinyl ether and tribromethanol are delayed, and in many instances in which anesthesia has not been prolonged, hepatic changes are not found. It might be mentioned herein that etherization of patients suffering from hyperinsulinism often will control that condition for several hours.

Anemic or Debilitated Patients.—It has become our practice to administer oxygen during prolonged anesthesia produced by pentothal sodium or to patients who are somewhat debilitated and anemic. We feel that in these instances in which respiration has been somewhat depressed by the effect of the anesthetic agent, the patient would derive much benefit from the inhalation of a high percentage of oxygen. Ravdin has pointed out that in hepatic disease there is often poor circulation of the blood through the liver. If anoxemia is allowed during anesthesia or if the blood is not well oxygenated, additional anoxemia in the liver may result in greater hepatic damage.

Nitrous Oxide-oxygen and Pentothal Sodium.—It has also become our policy to combine 50 per cent. nitrous oxide with 50 per cent. oxygen as a mixture for many patients who are to receive pentothal sodium intravenously. We have found that for the occasional patient who requires much pentothal sodium to maintain anesthesia, the addition of this mixture of gases by inhalation will materially decrease the amount of pentothal sodium required. In such an event, again, we are providing protection to the liver, for as has been previously pointed out, a high concentration of oxygen given with the anesthetic agent affords almost as much protection to the liver from the various anesthetic drugs as do solutions of glucose administered intravenously and preoperatively. This procedure also reduces the total amount of pentothal sodium administered.

Balanced Anesthesia.—Balanced anesthesia has been advocated for many years (19). Other combinations of types of anesthesia seem also to be of benefit to the patient, such as a combination of a small spinal or regional anesthesia and one of the anesthetic gases, or pentothal sodium. We believe there is definite advantage to be gained by administering a high concentration of oxygen to patients under spinal anesthesia, especially if there has been a sharp decrease in blood pressure with a consequent slowing of the vascular stream. It has been noted in many instances that nausea, vomiting and cyanosis will disappear if oxygen is administered and often there is some increase in blood pressure as a result of the use of oxygen. In cases in which a sharp decrease in blood pressure has taken place, 25 mg. of ephedrine

may be administered intravenously to support vascular tone. This in itself will go a long way toward preventing the occurrence of a damaging anoxemia. It is important to keep the blood pressure somewhere near a normal value and to keep the blood stream well oxygenated, especially when spinal anesthesia has been given to patients suffering from hepatic diseases, for a few minutes' anoxemia may greatly increase the postoperative morbidity by additional hepatic damage.

Anoxemia quickly damages the colloidal membrane of the kidneys, allowing the epithelium of the glomeruli to become permeable to protein, albumin and blood. This fact emphasizes the absolute necessity for constant prevention of the development of anoxemia regardless of the type of anesthetic agent being used. Constriction of the renal veins will result in an elevated glomerular pressure, with a resultant reduction of blood flow through the kidneys. This in itself may cause damaging anoxemia. Anesthesia itself may produce such an effect through its action on the circulation. This action may be the result of direct stimulation by the anesthetic agent or it may be the result of stimulation brought about by an excess amount of epinephrine which is liberated into the blood stream during the excitement stage of anesthesia.

Pentothal Sodium and Ether.—It might be well to use a small amount of pentothal sodium for the induction stage of anesthesia in patients who are to receive anesthesia with ether, especially if the patient has some degree of nephritis, for in this way the excitement stage with a consequent elevation of blood pressure can be almost entirely eliminated. It is perfectly true that anesthesia produced by pentothal sodium in itself suppresses urinary output, but for induction purposes the amount of pentothal sodium required probably would have very little effect on the excretion of urine from the kidneys.

Reduction of the Alkali Reserve.—It is pointed out in experimentation that young animals tolerate ether anesthesia very well without apparent renal damage and without an appreciable lowering of the alkali reserve of the blood. The opposite is true of older animals, for they show a great deal of renal damage following prolonged anesthesia produced by ether and there is a marked lowering of the blood alkali reserve. The results of this work should be carried over into clinical practice, for it seems reasonable that the same results would be found in a study on children and aged adults. Care should be taken whenever aged adults are anesthetized to prevent the loss of alkali reserve. This could be done by the preoperative intravenous administration of either a weak solution of glucose or a weak solution of sodium bicarbonate.

Patients Who Have Nephritis.—The anesthetist should always be alert when nephritis exists in the patient to be anesthetized. Anesthesia produced by tribromethanol or chloroform should never be used in a patient who is suffering from any degree of nephritis, for the possi-

bility exists that increased damage to the kidneys might occur, with resultant increased morbidity and possibly a mortality.

It is not enough to know that a particular agent may be used without disaster; the choice must be made so as to avoid those agents that are known frequently to give untoward results that may be fatal. A low mortality and morbidity rate is important in making a choice. Such a rate is concerned with both the immediate and remote untoward results of the administration of the anesthetic agent.

SUMMARY AND CONCLUSIONS

In summing up the results of these various investigations, the anesthetist should become impressed with the importance of always being thoroughly familiar with the condition of his patient. The anesthetist must be a good internist as well as a good technician, for it is his responsibility to evaluate the facts in the case as well as the requirements of the surgeon. Often a surgeon will order a certain type of anesthesia, perhaps because the operation seems simple or possibly because he likes that particular type of anesthesia, possibly because he may even be relenting to the patient's wishes. This method of choice of the anesthetic agent may be disastrous. The surgeon occasionally is unfamiliar with the toxic actions and disastrous sequelae of some anesthetic agents. It should become the responsibility of the anesthetist to absorb and study the facts in each case before an anesthetic agent is administered. If the surgeon's request can be granted without serious effects to the patient, well and good, but if a diseased or impaired condition of the liver or kidneys does exist and certain methods and agents are contraindicated, the anesthetist should remind the surgeon of the possibility of further damage to the patient. If this system is utilized, most surgeons will be glad of the cooperation they receive from their anesthetists and will be only too willing to cooperate, for, after all, the final result obtained in a surgical operation often depends as much on the anesthesia as it does on the surgical treatment and the postoperative care.

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At the regular session of the House of Delegates of the New York State Medical Association held in New York City, May 6, 1940, a resolution was adopted unanimously granting a Section on Anesthesia in the State of New York.

CONVULSIONS DURING ANESTHESIA[1]

An Experimental Analysis of the Role of Hyperthermia and Respiratory Acidosis

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The majority of authors who have considered the etiology of convulsions which occur during anesthesia have been concerned with an attempt to establish a single causative factor or agent. The few experimental inquiries have been directed to the same end. No convincing argument or evidence has been presented to establish such a single factor, although a large number of physiological and biochemical variables have been considered. This might lead one to suspect that several factors summate to effect the increase in cerebral irritability or reflex excitability required to induce convulsions in the presence of a high concentration of an anesthetic agent in the body. The relative infrequency of occurrence and the fact that convulsions may occur during anesthesia with any agent support this view.

It has not been established whether the increased level of irritability is caused by certain primary conditions inherent in the individual or by secondary factors from disease or from the anesthesia or operative procedure. This should be known in order to establish a basis for prevention and therapy.

No attempt will be made to review the literature here, since good recent reviews are available (2, 3). In the following outline, however, an effort has been made to organize into an orderly schema the more important factors cited in the literature as being of possible etiological significance. Certain factors have been proven to be present in a sufficient number of clinical cases to make them worthy of especial consideration in any experimental approach to the problem. These have been italicized.

A. Present Before Anesthesia.

1. Specific factors associated with the nervous system.
   - *a.* Individual susceptibility—*youth,* convulsive diatheses (epilepsy or spasmophilia).
   - *b.* Cerebral effects of disease—edema, vascular pathology, *specific organisms,* or neurotoxins.

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2. Non-specific factors affecting cerebral irritability which result secondarily from disease or toxemia.
   a. Calcium deficiency, ketosis, alkalosis, thymic syndrome, *fever,* renal insufficiency, autonomic nervous system imbalance, abnormal metabolic states.

B. RELATED TO ANESTHESIA OR SURGERY.

1. Impurities in anesthetic agent.
2. Modifications of the internal and/or external environment by drug action, technical methods, or surgical procedures.
   a. Anoxia, faulty carbohydrate metabolism, temporary renal insufficiency, acid-base imbalance (*metabolic and respiratory acidosis*), abnormal distribution of body water and osmotically active ions, *defective heat regulation, high environmental temperatures,* reflexes from operative trauma, etc.

A simple practical solution to the problem would be to assign the etiology to any one of the possibilities cited under *A*. The anesthetist would thereby be absolved if convulsive phenomena and death did occur since none of these factors is specifically under his control. It is impossible, however, to deny the existence of certain basic, but non-specific, conditions which are not only known to be present in many cases but also to be capable of inducing convulsive seizures. It seems reasonable, therefore, to determine experimentally whether any of the factors or combinations of factors cited under *B* are capable of producing the phenomenon in the normal individual or animal during anesthesia. Positive findings would not necessarily eliminate from consideration those factors listed under *A* or deny their possible etiological significance as contributing factors. Findings of a positive nature would, however, point out which factor or factors are to be controlled or avoided by the anesthetist or surgeon in order to prevent a further increase in the cerebral irritability.

Impurities in the agents used for anesthesia have been fairly well ruled out and will not be considered here. Impurities and degradation products have been found in a few instances, and it cannot be denied that if present these substances may have etiological significance. It is known definitely, however, that convulsions can and do occur during anesthesia performed with relatively pure agents.

A survey of the clinical case histories of reported convulsions during anesthesia, the pharmacology of anesthesia, and the technical methods in present use led to the conclusion that the most likely physiological mechanisms to be affected, either as a result of disease or from the anesthesia, were those concerned with heat regulation and the maintenance of the acid-base equilibrium. It appeared, furthermore, that deviations would be usually, in the first instance, toward a state of

hyperpyrexia, and in the latter, toward an increase in tissue acidity. Significant deviations from normal, in either case, are known to result in an increased irritability of the central nervous system, as indicated by the appearance of convulsions.

The experiments reported here have been designed to determine whether hyperthermia and carbon dioxide, alone or combined, were capable of inducing convulsions in the normal animal during ether anesthesia. In a few experiments the animals were rendered abnormal by subjecting them to a definite stress, such as starvation, before the experiment. Rats and dogs were used as the experimental animals.

METHOD

A closed circuit apparatus of large volume (645 liters), consisting of the anesthesia chamber (135 liters), two tanks (410 liters), and a Tissot spirometer (100 liters), was used in order that relatively constant gas concentrations could be maintained during the experiment. The components of this system were connected in series and circulation was maintained by a water-driven fan with a vertical shaft constructed in such a manner that the single bearing was submerged in water to prevent possible ignition of the explosive mixtures used. The circulating gases could be shunted around the anesthesia chamber while they were being thoroughly mixed in the remainder of the system. It was possible to increase the concentration of any constituent gas slowly during the experiment or expose the animal suddenly to a fixed concentration. The temperature within the anesthesia chamber could be maintained at a relatively constant level by heating devices placed outside the chamber. In the experiments in which the animals were anesthetized before being exposed to carbon dioxide or heat, a rectal thermometer was placed in position to allow readings during the experiment. In other experiments rectal temperatures were obtained at the end of exposure.

In the experiments on the dog, the anesthesia chamber was removed from the circuit and the animal connected by means of a short airtight endotracheal tube to the gas mixture which circulated in the remainder of the system.

Chemical determinations of ether concentrations were not made but constancy from one experiment to another was obtained by rapidly volatilizing an exact quantity of ether into the circuit. An approximate estimation of the ether concentration, which correlated reasonably well with depth of anesthesia, as judged by signs, could be made by observing the increase in the volume of the spirometer when the ether was volatilized. Determination of the carbon dioxide and oxygen content of the inspired atmosphere was made by the method of Van Slyke and Sendroy (4) after preliminary removal of ether by bubbling the gas through concentrated sulfuric acid.

RESULTS

Experiments on the Albino Rat.—Data on over three hundred experiments on rats have been obtained. Some animals were used more than once but never without an interval of several days. The individual experiments were usually conducted with groups of six animals. Three main variables were studied: ether anesthesia, environmental heat, and carbon dioxide. They were used singly and in all possible combinations by varying the sequence of exposure. The duration of the experiments varied from 30 to 150 minutes. A summary of the results is presented in table 1. Those animals in which clonic convul-

TABLE 1

SUMMARY OF EXPERIMENTS ON THE RAT

Conditions of Experiments	Total Animals	No Abnormal Muscular Activity	Incoordinate Muscle Twitchings	Clonic Convulsions
Heat 35–40° C. 2 hours	30	30	0	0
Ether 4–5%. 60–120 minutes	17	16	1	0
Ether + Heat (as above)	18	0	0	0
* CO_2 below 18% (O_2 20–23%)	28	0	0	0
CO_2 above 20% (O_2 20–23%)	24	0	22	2
CO_2 about 15% (O_2 7–10%)	18	0	0	0
CO_2 (O_2 65–70%)	12	9	3	0
Heat 1–2 hours + CO_2	18	0	0	0
Heat + CO_2 (O_2 8%)	6	0	0	0
Ether 3–5% + CO_2	24	19	5	0
Heat and CO_2 + Ether	54	26	25	3
Heat and Ether + CO_2	46	17	15	14

* See Fig. 1 for exact CO_2 concentrations.

sions developed are easy to define in the summary. Animals exhibiting muscular phenomena of any other type, from twitchings of small muscle groups to incoordinate jerking movements of one or more extremities, are included in the remaining group.

With the exception of one animal which exhibited a few twitchings, muscular activity was absent during ether anesthesia alone and during ether anesthesia conducted at environmental temperatures of 35 to 40° C. No abnormal muscular activity was observed in the normal unanesthetized rat at environmental temperatures of this order.

All of the experiments in which CO_2 was used are shown graphically in Fig. 1. Concentrations of CO_2 below 20 per cent. usually do not elicit muscular phenomena in the rat whereas exposure to higher concentrations may result in convulsive manifestations. The exact level is not easy to define because of individual variation. Concentrations exceeding 30 per cent. result usually in immediate depression and, in some instances, narcosis. Fifteen per cent. carbon dioxide was used as a standard in a majority of the experiments involving another variable

since a muscular response was never observed in the rat at this concentration of CO_2 alone.

Variations in oxygen concentration from 7 to 70 per cent. did not affect the response of the rat to 15 per cent. CO_2. Although the animal is restless after exposure for four hours to 8 per cent. oxygen there is no increase in muscular activity when exposed to 15 per cent. CO_2.

Heat alone or in combination with 8 per cent. oxygen did not alter the response to 15 per cent. CO_2.

Five of 24 etherized rats were observed to have muscular twitchings when exposed to 15 per cent. CO_2. Previous dehydration (water withheld 65 hours) or starvation (69 hours) did not affect the muscular response of the etherized rat to 15 per cent. CO_2.

These control experiments indicated, therefore, that when any of the three variables studied, ether, heat, and CO_2 (15 per cent.), were

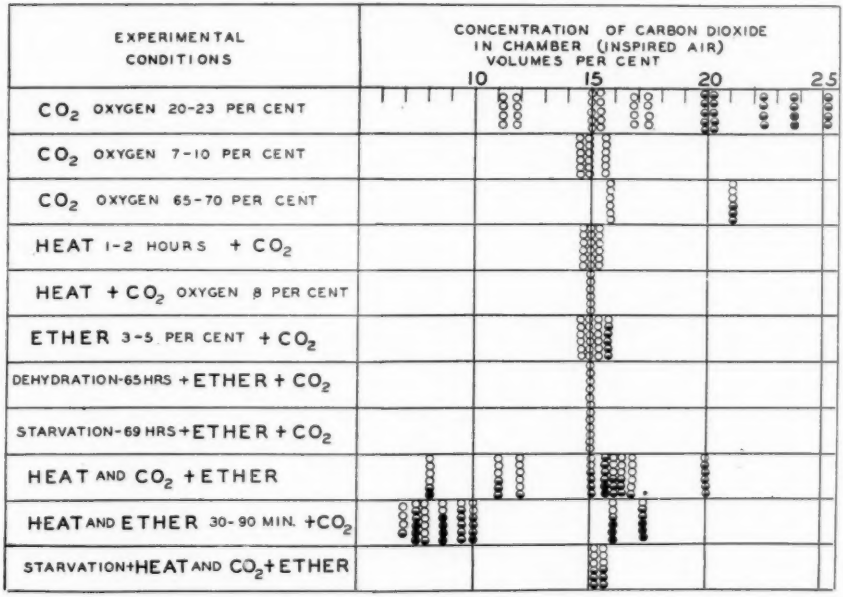
EXPERIMENTAL CONDITIONS
CONCENTRATION OF CARBON DIOXIDE IN CHAMBER (INSPIRED AIR) VOLUMES PER CENT
10
15
20
25
CO2 OXYGEN 20-23 PER CENT
CO2 OXYGEN 7-10 PER CENT
CO2 OXYGEN 65-70 PER CENT
HEAT 1-2 HOURS + CO2
HEAT + CO2 OXYGEN 8 PER CENT
ETHER 3-5 PER CENT + CO2
DEHYDRATION-65 HRS + ETHER + CO2
STARVATION-69 HRS + ETHER + CO2
HEAT AND CO2 + ETHER
HEAT AND ETHER 30-90 MIN. + CO2
STARVATION + HEAT AND CO2 + ETHER

FIG. 1. Graphic representation of all experiments involving exposure to CO_2 showing the type of muscular response of each individual rat and the concentration of CO_2 at which the experiment was conducted. *Unfilled circles*—no abnormal muscular activity. *Half-filled circles*—incoordinate muscle twitchings or jerking. *Filled circles*—clonic convulsions.

exhibited singly, or in any dual combination, an increase in muscular activity was observed only in those experiments in which the etherized rat was exposed to carbon dioxide.

Results which appear to have much greater significance were obtained, however, when all three factors were combined. Not only did the incidence of muscular twitching increase greatly but also definite

convulsive seizures occurred in a significant number of experiments even though the concentration of carbon dioxide was reduced to 7.5 per cent. (Fig. 1). Furthermore, the combination of these three factors in a certain sequence of exposure resulted in a further increase in the incidence of convulsions. It will be observed from Fig. 1 that simultaneous exposure to heat and CO_2 followed by anesthetization with ether was much less favorable for the production of convulsions than the simultaneous administration of ether and heat followed later by the sudden exhibition of CO_2.

The incidence of convulsions in these experiments was greatest when the rat was anesthetized with ether at an environmental temperature of 35 to 40° C. for thirty to ninety minutes, during which time the body temperature of the animal was increased 2 to 4° C., and was then exposed suddenly to relatively high concentrations of CO_2 (7.5 to 10 per cent.). A representative protocol of an experiment of this type is presented in Table 2. In this experiment the concentration of CO_2

TABLE 2

EFFECT OF PYREXIA AND HYPERCAPNIA ON ETHERIZED RAT (REPRESENTATIVE PROTOCOL)

9:30 a.m.	6 Rats Anesthetized in Chamber (Temp. 35° C.). Atmosphere: Oxygen 24%; Nitrogen 72%; Ether 4% (approx.).
10:00 a.m.	Carbon Dioxide Added (Chamber Temp. 38° C.).
10:05 a.m.	Rat 1—Rectal Temp. 41.7° C.—Generalized Convulsion.
10:06 a.m.	Rat 2—Rectal Temp. 43.5° C.—Generalized Convulsion.
10:09 a.m.	Rat 3—Rectal Temp. 43.3° C.—Twitching of Extremities.
10:11 a.m.	Rat 4—Rectal Temp. 42.8° C.—Generalized Convulsion.
10:13 a.m.	Rat 5—Rectal Temp. 44.0° C.—Twitching of Face and Head.
10:14 a.m.	Rat 6—Rectal Temp. 45.0° C.—Dead. No Convulsions.
10:14 a.m.	Gas Sample Obtained.
	Oxygen ..... 22.7 per cent.
	Carbon Dioxide ..... 7.62 per cent.
10:15 a.m.	Rats Removed from Chamber (Chamber Temp. 39.5° C.)
10:35 a.m.	Rat No. 1 waking; Rats Nos. 2, 3, and 6 dead. Rats Nos. 4 and 5 died later.

necessary to induce convulsions was only 7.5 per cent. The possibility exists that lower concentrations of CO_2 would have been effective although they were not tried.

Thirty-four animals were subjected to ether anesthesia at temperatures between 35 and 40° C. and subsequently exposed to 10 per cent. CO_2 or less. Sixty per cent. exhibited some type of muscular activity during the procedure including 20 per cent. which developed definite convulsive seizures. The incidence was slightly greater at higher concentrations of CO_2.

Experiments on the Dog.—Experiments of a similar nature were performed on thirteen dogs during ether anesthesia. The results are tabulated in Table 3. As these animals were not placed in a chamber of uniform temperature but heated by coils placed beneath the dog board, the two series of experiments are not exactly comparable.

TABLE 3

EFFECTS OF CARBON DIOXIDE AND HYPERPYREXIA ON ETHERIZED DOG

Dog	Duration of Anesthesia	Rectal Temp.		Atmosphere		Muscle Activity During Anesthesia
		Initial	Final	CO_2	O_2	
	min.	°C.	°C.	vol. %		
119	93	40.0	42.5*	7.7	24.0	None
118	110	39.0	42.2*	7.9	22.0	None
102	60	39.5	41.8	8.2	23.2	Twitching—Forelimbs.
109	115	39.0	41.7	10.6	18.6	Jerking Extremities.
108	160	39.0	42.3	10.8	24.2	Jerking Extremities.
115	190	39.0	40.7	10.8	22.0	Jerking—Hind limbs.
107	150	38.2	41.3	11.0	22.2	Neck, Back, Extremities.
120	140	39.0	42.5*	13.7	19.8	Intermittent—Hind limbs.
104	59	38.0	42.5	16.0	23.9	Clonic Convulsions.
103	70	38.0	41.3	16.3	23.9	None
111	110	38.5	41.6	16.8	20.0	Incoordinate—Hind limbs.
105	110	38.5	41.5	17.2	20.3	Jerking—Extremities.
106	155	38.5	41.4	18.6	17.6	Twitching—Hind limbs.

* By Electromagnetic Induction.

Judging from changes in rectal temperature, however, similar grades of pyrexia were induced in the dog as in the rat. These experiments were not so well controlled as those in the rat, since no attempt was made to determine the exact convulsant level of carbon dioxide for this animal. Conclusions were based entirely on the presence or absence of muscular phenomena when the three basic variables were used.

The results are somewhat less striking than those obtained with the rat. In only one instance were generalized clonic convulsions induced in this series of thirteen animals. Evidence of increased muscle activity of a more localized nature was present, however, in all but three animals. These changes varied from twitchings of isolated muscle groups to movements involving one or more limbs. It seemed evident from the appearance of these animals that a slightly further increase in irritability would have precipitated a generalized convulsive seizure. In most of the experiments the level of anesthesia was approximately second plane of the third stage, a depth not so great as that used in the rat.

In a few experiments fever was produced by electromagnetic induction. Some of these experiments are included in Table 2. No essential difference was observed.

Convulsions during Anesthesia with Cyclopropane.—The experiments just outlined were conducted with ether since a majority of clinical cases reported in the literature have involved the use of this agent.

During the course of experiments reported previously (5), rabbits and dogs were anesthetized with cyclopropane in a closed circuit device in which the carbon dioxide was absorbed by soda-lime. In two in-

stances, one each with a rabbit and a dog, the inadvertent use of partially exhausted soda-lime resulted in an accumulation of carbon dioxide in the circuit. In both experiments convulsions were observed as the first manifestation of these errors. By coincidence the environmental temperature in both experiments was high as they were conducted during the summer months. In these experiments it was possible to determine the tension of carbon dioxide not only in the inspired air, but also in preformed depots of air in the skin and peritoneal cavity. The results in these two experiments are shown in Table 4.

TABLE 4

CONVULSIONS OCCURRING DURING CYCLOPROPANE ANESTHESIA

	Cyclopropane Anesthesia		Carbon Dioxide Final Concentration		Result
	Duration	Final Concentration	Inspired*	Tissue Depot	
	min.	volume %	volume %	volume %	
Rabbit 46	284	15	4	24 (skin)	Convulsions lasting intermittently for 30 minutes. Survival.
Dog M	105	18	13	34 (skin) 31 (peritoneum)	Clonic convulsions 5 minutes duration. Intense hyperpnea for 50 minutes. Survival.

* Atmosphere contained over 50 per cent. oxygen in both experiments.

The pressure of carbon dioxide in these gas depots in the tissues was remarkably high and can hardly be explained except on a basis of a diminished blood flow to the parts involved. It may be that similar changes in blood flow occur to other more essential areas of the body such as the brain and spinal cord.

DISCUSSION

The results of these experiments support the premise that several factors, usually incapable of inducing convulsions during anesthesia if acting singly, may summate to produce such an effect even in the normal animal.

The two factors studied in these experiments, heat and carbon dioxide, have been previously indicted and there is reasonably good clinical evidence to support the argument that their relationship to the convulsions of anesthesia is causal.

Hadfield (6), Wright (7), Smith (8), Woolmer and Taylor (9), Bull (10) and others have supported the view that pyrexia is an important etiological factor. Their arguments may be presented in the following manner. Fever, usually secondary to an acute toxemia, is present in

a large majority of reported cases. Metabolic activity, and hence heat production, is significantly increased by the fever. The heat regulatory mechanisms, abnormally adjusted by the existence of fever, are inactivated further by the narcotic agent. An abnormally high body temperature must result, if at this time, when heat production is maximal and heat regulation defective, heat dissipation is greatly reduced by the anhidrotic action of atropine, by procedures such as the application of rubber blankets, the administration of anesthetic agents at summer temperatures, or causing the patient to breathe heated atmospheres. Finally, it is well established that convulsions are associated commonly with the excessive pyrexia of heat stroke.

Proof that hyperpyrexia alone is sufficient to induce convulsive seizures during deep anesthesia would be more convincing than the most logical argument. It is to be noticed that the experiments described here did not adduce this proof although they did demonstrate that fever resulted in an increased cerebral irritability during anesthesia as judged by the increased response to carbon dioxide.

Pinson (11) was one of the first to discuss the possible role of carbon dioxide as a convulsant during anesthesia. He emphasized that convulsions are usually preceded by inadequate, jerky or sterterous respiration, and states:

"I have come to regard the convulsion as largely the outcome of the extensive action of carbon dioxide in patients who are sensitive to this naturally or by reason of toxemia, pyrexia, and so on, and who are under the influence of ether, a substance itself having a marking effect on breathing. . . . Treatment based on this assumption has so far been successful. It is directed to the riddance of excess carbon dioxide and must be prompt."

Waters (12) holds to the view that carbon dioxide is the usual inciting factor and stresses the necessity of adequate ventilation and the elimination of rebreathing in prevention or treatment.

In this discussion of the relation of carbon dioxide to convulsions, the implication is that a significant respiratory acidosis exists, either as a result of decreased respiratory activity or exposure to a high concentration of carbon dioxide from rebreathing. This necessitates a closed or semi-closed system or deep anesthesia or both. It is hardly necessary to point out that no significant increase in the carbon dioxide content of tissues occurs during the administration of small concentrations of this gas to a subject whose respiratory "centers" are capable of responding to the stimulus by a commensurate increase in ventilation, providing a technic is used in which rebreathing is prevented.

It is well established that carbon dioxide in high concentration (20 to 30 per cent.) will induce convulsions in the anesthetized normal human subject (13). It is not reasonable, however, to believe that concentrations of carbon dioxide of the order required to induce convulsions in the normal anesthetized human subject are present in all cases

of convulsions during anesthesia. Therefore, it seems logical to search for factors which increase the response of the subject to carbon dioxide. It has been demonstrated in the experiments described here that pyrexia is such a factor.

Other factors must exist also. If it is assumed that the action of carbon dioxide is non-specific, and that convulsions result from an increase in the H-ion concentration of blood and tissues to a certain threshold level, then the existence of a metabolic acidosis (diminished alkali reserve) should lower the concentration of carbon dioxide required to effect such a level of H-ion concentration, since the cations available to bind carbon dioxide as carbonate or bicarbonate would be reduced.

A certain significance is attached to the fact that a large majority of the factors which have been indicted to account for convulsions during anesthesia result either in a metabolic or a respiratory acidosis, i.e., they increase the H-ion concentration in blood and tissues. Some of these factors have been summarized in Table 5.

TABLE 5

CHARACTER OF ACID-BASE IMBALANCE PRODUCED BY CERTAIN FACTORS OF POSSIBLE ETIOLOGICAL SIGNIFICANCE IN CONVULSIONS WHICH MAY OCCUR DURING ANESTHESIA

Metabolic Acidosis	Respiratory Acidosis
1. Anoxia.	1. Depressant effect of premedication and/or anesthetic agent on respiration.
2. Starvation.	2. Rebreathing (dead-space in mask, connectors, or apparatus; soda-lime exhaustion).
3. Abnormal metabolic states (ketosis, etc.).	3. Carbon dioxide administration by closed or semi-closed technic.
4. Renal insufficiency (permanent or temporary).	4. High oxygen atmospheres (acid oxyhemoglobin diminishes transport of CO_2).
5. Dehydration.	
6. Improper carbohydrate metabolism.	
7. Prolonged hyperventilation from fever—compensatory increase in fixed acids and loss of base.	
8. Specific acids (mandelic, etc. administered therapeutically).	

In this outline no attempt has been made to separate those factors which accompany disease and those which may occur as a result of the anesthesia or operation since, in many instances, they would summate.

A suggestive case, previously reported, which lends support to the view that a preexistent metabolic acidosis sensitizes the subject to carbon dioxide, occurred on the anesthesia service of the Wisconsin General Hospital (14). A girl, age 12, was scheduled for tonsillectomy. She had been receiving ammonium mandelate for two weeks prior to the operation in the treatment of pyelitis. Fluids had been limited. The urine pH ranged about 5.5. Thirty hours before operation the ammonium mandelate was discontinued and fluids were increased. Anesthesia was induced with open drop ether and an endotracheal tube

was inserted. This was connected to a small bag and some rebreathing was permitted. Twelve minutes later a generalized convulsion occurred. The treatment which was effective consisted solely in the elimination of rebreathing and institution of artificial respiration.

The argument that carbon dioxide cannot be of etiological significance since "convulsions are not ushered in by cyanosis" (6, 15) is entirely fallacious. Carbon dioxide in high concentration in the presence of adequate oxygen does not induce cyanosis. On the contrary, a carmine pink color is the rule.

The views of Collip and Backus (16) and Kemp (17) which relate convulsions to alkalosis from hyperventilation induced by the agent are at variance with those presented here. Recent evidence (18, 19) indicates rather clearly that acute and severe respiratory alkalosis during anesthesia both in the dog and man does not induce convulsions. On the other hand, prolonged hyperventilation before anesthesia such as might result from fever, could by virtue of the compensatory increase in fixed acids and renal excretion of base which occurs, render such a subject more sensitive to the convulsant action of carbon dioxide when the latter was exhibited suddenly in high concentration during anesthesia.

It is not the intention of the authors to advance any new hypothesis to explain the convulsions of anesthesia, to support any single etiological factor to the exclusion of all others, or to deny the possible contribution of certain "idiopathic" elements. It is reasonable to assume that a nervous system with a higher level of metabolism and irritability, such as is normally present in the child, or which may be present in the adult as a result of specific constitutional factors, disease or toxemia, should respond to a lesser stimulus than that required in the normal subject.

In the present state of knowledge it is not deemed desirable to indulge in a discussion of the problem of convulsions as it relates to the more basic concepts of transport and availability of substrates and oxygen to, and utilization by, the nerve cell although it is appreciated that these, as yet poorly defined, mechanisms are probably involved in a most intimate fashion. We must be content at present to express the belief that the incidence of convulsions during anesthesia, certainly those with fatal termination, could be reduced to an insignificant figure if (*a*) attention were directed to the vicarious regulation of a reasonably normal temperature during anesthesia; (*b*) appropriate procedures were adopted to control all cases in which an uncompensated metabolic acidosis exists either before or during anesthesia; (*c*) measures were taken to prevent the development of a severe respiratory acidosis during anesthesia. The evidence is reasonably good that carbon dioxide in many cases serves as the immediate stimulus to precipitate convulsive manifestations.

SUMMARY

Convulsions or muscle twitchings are seldom observed in rats or dogs when exposed singly to any one of the following conditions: ether anesthesia, an environmental temperature of 35–40° C., carbon dioxide to 15 per cent. Muscle twitchings were observed in twenty per cent. of etherized rats exposed to 15 per cent. CO_2. This was the only dual combination of these three factors which resulted in muscular activity.

Fever induced by exposing the etherized rat to temperatures of 35–40° C. renders this animal sensitive to the convulsant action of carbon dioxide. Sixty per cent. of etherized rats rendered hyperpyretic (rectal temperature 41–44° C.) and exposed to concentrations of CO_2 below 10 per cent., exhibited abnormal muscular activity of some type, including twenty per cent. which developed clonic convulsions. Similar but less striking results were obtained in the dog.

A critical analysis of the clinical evidence bearing on the etiological significance of hyperpyrexia and respiratory acidosis is presented. Discussion is directed primarily to the premise that fever and numerous other factors, particularly those which produce a metabolic acidosis, increase the cerebral irritability to such a level that a rapidly induced respiratory acidosis, whether from respiratory depression, rebreathing, or the administration of carbon dioxide, serves as an adequate stimulus to induce convulsions during anesthesia.

The authors are indebted to Dr. B. L. Boynton for assistance in some of the experiments.

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At the regular meeting of the King's County Medical Society held March 19, 1940, the following resolution was adopted:

Be it Resolved that in order to better serve the hospitals with which they are connected and, to improve that service by greater co-operation and understanding, the Joint Council of Pathologists, Radiologists, Anesthesiologists and Physical Therapy Physicians recommends that all Grade A Hospitals shall have physicians, especially trained in Pathology, Radiology, Anesthesiology and Physical Medicine, in charge of these departments and that the Directors of these departments shall be members of their respective Medical Boards, with the power to vote, and WHEREAS at the same meeting of the King's County Medical Society their delegates to the New York State Medical Society were instructed to present and support the above resolution, therefore

Be it Further Resolved that in those areas of the State of New York in which the above specialties are not represented by specialists it shall be permissible for physicians trained in these specialties to represent the specialty of their respective medical boards.

Be it Resolved that the House of Delegates of the New York Medical Society at its regular session of May 6th, 1940 does hereby approve this resolution, and

Be it Further Resolved that this resolution shall be presented to the House of Delegates of the American Medical Association at its next meeting in New York City, June, 1940.

THE LOCAL ANESTHETIC PROPERTIES OF EPHEDRINE HYDROCHLORIDE [1]

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ALTHOUGH ephedrine has been used as a vasoconstrictor substance in association with local anesthetic agents, no detailed examination of this compound for local anesthetic properties has ever been reported. Recently, in connection with another investigation, it was observed that ephedrine produced anesthesia when injected intracutaneously into the human. This observation indicated that it would be of interest to subject ephedrine to the usual experimental methods employed for evaluating local anesthetics.

In all of the experiments described below, ephedrine HCl was dissolved in 0.73 per cent. NaCl.

Four-tenths of a cubic centimeter of the solutions of ephedrine were injected intracutaneously into the flexor surface of the forearm. The anesthesia was tested by noting the loss of sensation to pin pricks of the injected area as compared with the adjoining untreated skin. The subject, whose head was turned in such a manner that he was not able to see the area touched, reported his sensations to the operator. The minimal effective concentration of ephedrine was found, in four experiments, to be 0.1 per cent. of ephedrine HCl. Solutions of ephedrine were very irritating while being injected, but this effect disappeared soon after the injection had been completed. The average duration of anesthesia was 5 and 18 minutes, respectively, when 0.1 and 0.5 per cent. solutions of ephedrine were tested.

Ephedrine was then tested for its ability to block motor nerves. The excised sciatic nerve and gastrocnemius muscle of a frog were placed in troughs cut in a paraffin block. Ringer's solution bathed the preparation with the exception of a short length of the nerve trunk which was immersed in a solution of the drug. The excitability of the preparation was tested by applying to the distal end of the nerve, a simple break shock from the secondary coil of a Harvard inductorium which was set at 12 cm. Using this strength of stimulus on five preparations treated with five per cent. ephedrine, the average onset of anesthesia was 48 minutes.

If the secondary coil of the inductorium was set at the threshold "make" stimulus (20 to 26 cm.), the simple "break" shocks supplied at this setting were of considerably less strength than those supplied from

[1] This investigation was aided by the W. E. Weiss Fellowship Fund.

the above inductorium setting. Using this strength of stimulation, it was found that five per cent. ephedrine produced anesthesia in twelve minutes in four preparations and the duration was about eighty minutes, after which time there was complete recovery indicating the reversibility of the anesthesia.

Solutions of ephedrine were injected intraspinally into male winter frogs (*Rana pipiens*) according to the procedure of Bieter, Harvey and Burgess (1). The volumes injected were no greater than 0.15 cc. and no less than 0.03 cc. Each frog received no more than one injection. If the frog failed to withdraw his submerged hind feet from 0.5 per cent. hydrochloric acid in thirty seconds he was considered anesthetized. The minimal anesthetic dose, or the dose which produces spinal anesthesia in 50 per cent. of the animals, was found to be approximately 0.1 mgm./gm. of body weight. Using the same technique the minimal anesthetic dose of procaine HCl was found to be about 0.015 mg./gm. The results are shown in Table I.

TABLE I

THE ANESTHETIC EFFECT OF INTRASPINAL EPHEDRINE HCl

Dose mg./gm.	No. Frogs	Per cent. Anesthetized	Onset of Anesthesia (minutes)	Duration of Anesthesia (minutes)
0.03	8	12.5	4	80
0.05	8	37.5	2	149
0.10	11	55	4	>100
0.20	9	89	21	>100

An examination of the responses of the frogs twelve hours after the injections revealed that they had completely recovered from the effects of the ephedrine.

Concentrations of five and ten per cent. ephedrine produced no anesthesia of the rabbit's cornea.

The ephedrine HCl used in these experiments when checked for its purity in the polariscope gave a specific rotation of — 33 degrees. Samples from two different sources were examined for their effect by the human intradermal wheal method and there were no significant differences in the results.

Read and Lin (2) have shown that 0.01 per cent. ephedrine produces no anesthesia when injected intracutaneously. They were interested in its effect on the prolongation of local anesthesia. From this concentration, which is one-tenth of the threshold concentration found in this work, no anesthetic effect would be expected. They also noted that 0.005 per cent. ephedrine potentiated the action of procaine in blocking the sciatic nerve of the toad. They report that one per cent. ephedrine "kills" the sciatic nerve substance and lower concentrations lessen its conductivity to a slight extent. They concluded from these

experiments that ephedrine has no blocking effect. Since there is a reversibility of anesthesia in the sciatic preparations and the frogs injected intraspinally, it appears that ephedrine has an effect on nerve conduction other than that caused by the destruction of the nerve substance.

Summary.—Ephedrine HCl, in concentrations of five per cent., is capable of blocking the sciatic nerve of the frog. The minimal anesthetic dose of ephedrine HCl for spinal anesthesia in frogs is about 0.1 mg./gm. One-tenth of one per cent. of ephedrine produces anesthesia in the human when injected intracutaneously. All these effects are completely reversible.

The many helpful suggestions of Dr. Henry G. Barbour are gratefully acknowledged.

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A combined meeting of the Section on Anesthesia of the Connecticut State Medical Society and the American Society of Anesthetists, Inc., will be held in conjunction with the Clinical Congress in New Haven, Connecticut, on September 17, 1940, at 8:00 P.M.

The program will be:

(1) "Anesthesia for Operations About the Head" by Lloyd H. Mousel, M.D., Mayo Clinic, Rochester, Minnesota. (Tentative.)

(2) "Pentothal Sodium in Relation to Urologic Procedures" by Frederick Wilcox, M.D., Brooklyn Hospital, Brooklyn, New York.

(3) "Circulatory Effects from Traumatic Reflexes Stimulated During Abdominal Surgery" by E. A. Rovenstine, M.D., Bellevue Hospital, New York, New York.

THE PREVENTION AND TREATMENT OF POSTOPERATIVE PULMONARY COMPLICATIONS WITH SPECIAL REFERENCE TO SUCTION BRONCHOSCOPY

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ONE of the most serious problems related to the postoperative management of surgical patients is that of pulmonary complications. The frequency with which respiratory complications may develop even in patients with apparently no predisposing pulmonary pathology makes this an ever present menace confronting the anesthetist, the surgeon and internist.

For the purpose of this discussion the term "postoperative pulmonary complications" will be limited to those conditions usually known as pneumonia or pneumonitis, an atelectasis. There have been many theories advanced to explain the development of postoperative pulmonary complications and probably no single one of these theories accounts for all complications or is even entirely responsible for the development of any particular complication. It is a well known fact that postoperative pulmonary complications are more frequently seen following operations on severely ill or septic patients. This would seem to lend support to the theory that these complications are caused by septic emboli carried by the blood stream and becoming lodged in the lung issue. This theory is hard to reconcile with the clinical picture in most of these cases.

The clinical picture in these patients would certainly indicate that the primary focus of infection is in the air passages themselves and spreading from them to adjacent tissue. This is certainly compatible with the theory that these complications are caused by the inhalation of septic material while the patient is anesthetized. On the other hand, however, the frequency with which pulmonary complications follow spinal anesthesia and even local infiltration anesthesia tends to detract from the validity of this explanation of their development. It has been fairly well established that the development of postoperative pulmonary complications is influenced very little by the agent used to produce anesthesia.

The fact that pulmonary complications are more frequent following abdominal operations and particularly so following operations in the upper abdomen is in keeping with the theory that they are caused by decrease in aeration of the lungs resulting in an area of lowered resistance. There are many factors which contribute to decreased aeration

of the lungs, particularly of the lower lobes, following operations in the abdomen. There is always an elevation of the diaphragm after the abdomen has been opened, and the pain which may accompany any attempt at deep breathing will result in more shallow respiration, and of course, decreased aeration of the lungs. This condition may be further enhanced by constricting abdominal binders, or by depression of respiration from medication or from surgical shock. This area of lowered resistance, as a result of inadequate aeration, is then susceptible to attack by organisms which may have already been present or may have arrived by inhalation of septic material or by septic emboli. It is reasonable that one or all of these factors may play a part in the development of some postoperative pulmonary complications.

The clinical picture that is usually presented when postoperative pulmonary difficulties occur and the rapidity with which they develop seem to lend credence to the theory that most of these complications can be explained on an atelectatic basis with such of the other contributing factors as may play a part in the particular case. It seems that the most plausible explanation for the development of the majority of pulmonary difficulties occurring postoperatively is that there is an underlying bronchitis that may not have been brought out in the history. This bronchitis may be either infectious or chemical in origin. As examples of chemical bronchitis the chronic cough of smokers may be mentioned as well as the irritation that may result from certain inhalation anesthetic agents such as ether. This bronchitis is usually the cause of increased secretions which may become inspissated and form a plug in one or more of the respiratory passages. The gases distal to the plug will, of course, be eventually absorbed and an area of atelectasis will be the result. If to this condition we add such factors as decreased aeration of the lungs due to elevation of the diaphragm, respiratory depression, pain from an abdominal wound or tight abdominal binders, the stage is certainly set for the development of more serious complications. The accompanying diagram by Souders [1] (Fig. 1) is an attempt to demonstrate diagrammatically a probable chain of events which may take place in the development of more serious pulmonary complications in patients with bronchitis.

The course of events which may follow the development of one or more areas of atelectasis in the lung is very largely dependent on the amount of lung involved in the atelectasis and the promptness with which this conditions is relieved. If an entire lung is collapsed the condition is usually spoken of as massive collapse. When one lobe of the lung is involved it is known as lobar collapse, and if a smaller area of the lung than one lobe is involved the condition is known as lobular collapse. When one or more lobes of the lungs are suddenly collapsed the signs and symptoms at first are those that result from the actual mechanical changes in the chest. The symptoms are usually quite

[1] Souders, C. R.: Personal communication to the author.

sudden in onset, and are largely those of acute oxygen want. There is a sharp rise in temperature and in the respiratory rate. There may be evidence of considerable respiratory embarrassment and some degree

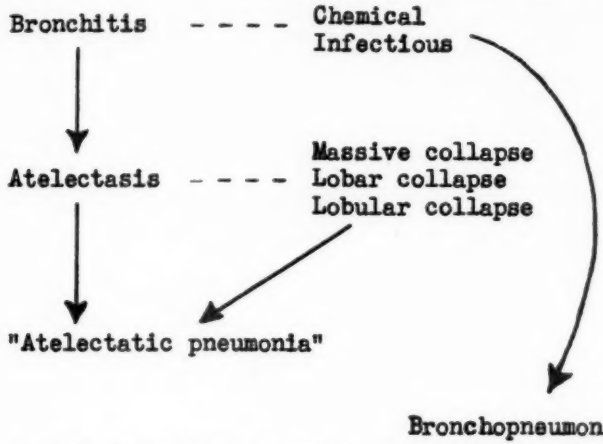

FIG. 1. Diagrammatic illustration of the probable course of events in the development of many postoperative pulmonary complications in patients with bronchitis.

of cyanosis is usually present. The roentgenologic picture shows decreased aeration of the lung on the affected side, with a shift of the mediastinum toward that side. There is usually an elevation of the diaphragm on the affected side.

When a smaller portion of the lung is involved such as one or more lobules, the symptoms are no so striking or so acute in onset. There is not such marked respiratory embarrassment and cyanosis may be only slight or even entirely absent. There is usually a rise in temperature, but this rise is not so sudden as when one or more lobes of the lung are involved. With lobular atelectasis the clinical course as well as the roentgenologic appearance of the chest may very closely simulate bronchopneumonia. There is little doubt that, if unrelieved, lobular atelectasis will eventually result in pneumonia. In fact, when any part of the lung is collapsed, certainly ideal conditions are present for the development of a pulmonary infection, namely, heat, moisture and organisms in an area of lowered resistance.

Because of the frequency with which serious pulmonary complications follow the development of areas of atelectasis, every effort should be made to prevent their development. Furthermore, prompt measures should be taken for their relief should they develop. The most important factor in the prophylaxis of pulmonary atelectasis is to prevent the accumulation of secretions in the respiratory passage. Frequently turning patients from side to side and urging them to cough is of value in the prevention of fluid accumulation in the tracheobronchial tree.

Drugs for the relief of pain and restlessness or to produce sleep, which may depress respiration, should be used cautiously. Obviously binders which restrict motion of the chest should be avoided. The value of atropine when there is a tendency toward accumulation of fluid in the respiratory passage is open to question. While this drug will very likely diminish the amount of secretion it will probably increase the viscosity of the fluid that is present, making it more tenacious and hence more likely to form a plug in the bronchus or bronchiole. Carbon dioxide inhalation is probably of little or no value in the prevention of postoperative pulmonary complications.

When there is an appreciable amount of fluid in the respiratory passages which the patient has demonstrated his inability to raise by coughing, active measures should be instituted to remove it. Occasionally simple aspiration of the respiratory passages by means of suction through a fairly large urethral catheter (22F) passed into the trachea will be sufficient to remove accumulated fluid. This catheter can best be passed through a nostril and guided into the trachea by means of forceps, with the larynx under direct vision through a laryngoscope. If the patient is conscious it is well to spray the nose, pharynx and larynx with a solution of cocaine (10 per cent) before this procedure. The paroxysms of coughing which are initiated by this procedure are of benefit in forcing the fluid out of the smaller bronchioles. Although simple aspiration through a catheter is frequently all that is necessary to remove accumulated fluid from respiratory passages, a more thorough and efficient aspiration should be performed if there is any definite area of atelectasis present. A method should be employed by which one can be sure that the offending material is removed. Thorough aspiration of the respiratory passages by means of suction bronchoscopy is certainly the surest and most efficient method of relieving atelectasis due to occlusion of an air passage.

The following case history with accompanying roentgenograms (Fig. 2) and temperature chart (Fig. 3), taken from a considerable group of cases in which this procedure has been employed, will serve to illustrate the very striking result that is sometimes seen following bronchoscopic aspiration of the air passages in patients suffering from postoperative pulmonary atelectasis.

Case Report 1.—A man, forty-six years of age, with extensive carcinoma of the stomach, was submitted to total gastrectomy. Convalescence for the first forty-eight hours after operation was quite satisfactory, the highest recorded temperature being 100° F. Although there was no sign of anoxemia, the patient was kept in an oxygen tent throughout this period. His respiratory rate ranged from 20 to 26. Quite suddenly on the morning of the second postoperative day he began to show signs of dyspnea. The respiratory rate increased to 40 and his temperature rose to 103° F. This condition became progressively worse during the next two hours before he was taken to the operating

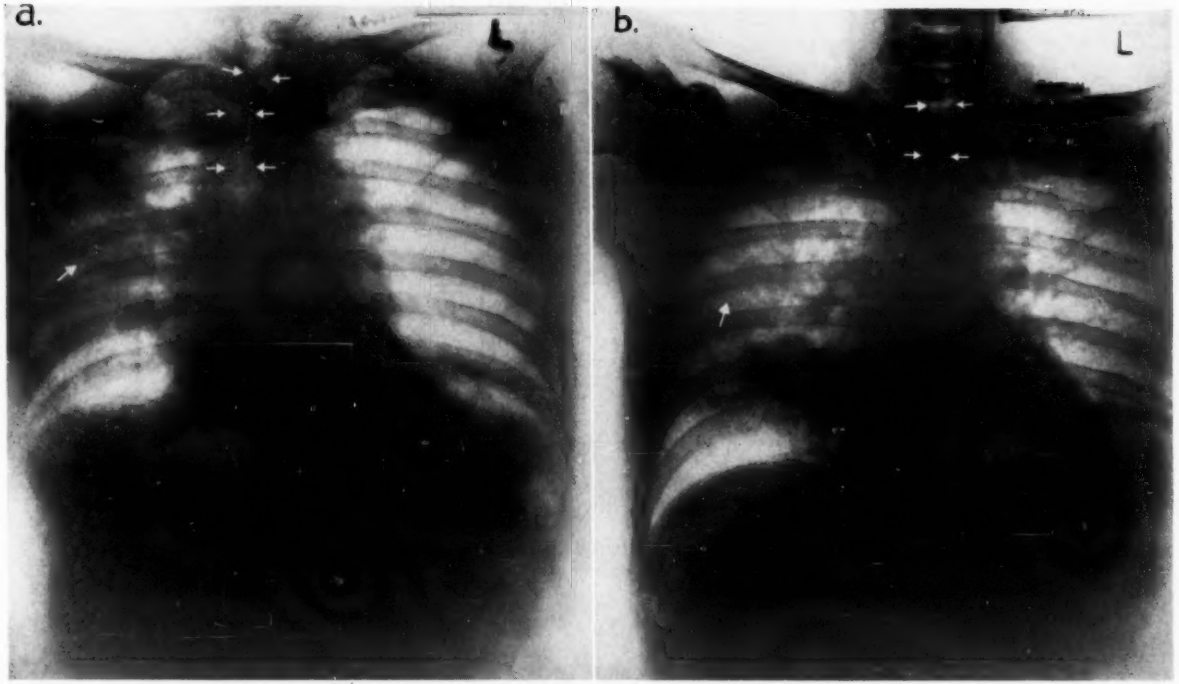

FIG. 2. Roentgenograms of chest in Case 1. In *a*, taken thirty minutes before bronchoscopy, note displacement of trachea to right and cloudiness of right lung field. *b*, Taken about four hours after bronchoscopy, shows trachea in almost normal position with considerable clearing of right lung field.

room for bronchoscopic aspiration of his air passages. During this time he became almost moribund and presented a grade 2 cyanosis even though he was in an atmosphere of over 50 per cent oxygen. A roent-

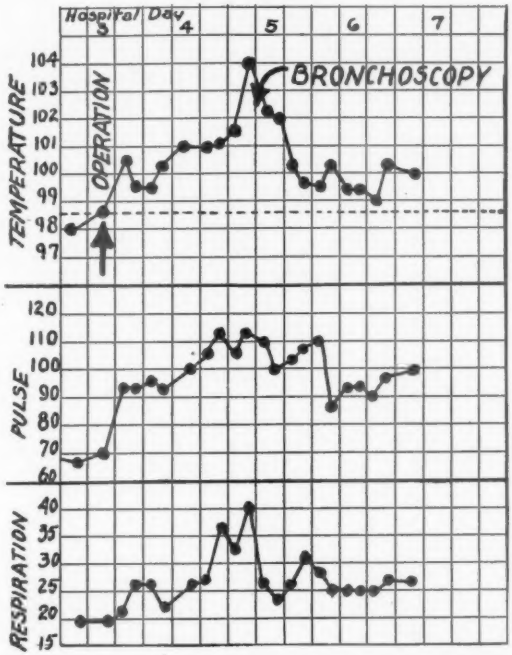

FIG. 3. Temperature chart in Case 1. Note rapid rise of temperature, pulse and respiratory rate, with equally rapid fall following bronchoscopic aspiration of tracheobronchial tree.

genogram (Fig. 2 *a*) taken at this time showed a shift of the mediastinum to the right, with an elevation of the diaphragm on this side, and multiple areas of atelectasis throughout the right lung field.

Thorough aspiration of the respiratory passages through a bronchoscope was performed with almost immediate relief of the acute symptoms. Thirty minutes after this procedure was completed the patient was quite alert and conversing with the patient in the adjoining bed. His cyanosis and dyspnea had all disappeared. A roentgenogram (Fig. 2 *b*) taken five hours after this procedure showed the mediastinum in the midline, and a decrease in the amount of atelectasis in the right lung. This patient had no further respiratory difficulty throughout the remainder of his convalescence and he was discharged from the hospital on the twenty-ninth day after operation.

While it is true that many plugs in the air passages will be spontaneously expelled if the patient is turned from side to side and urged to cough, some of them will not be until the patient had passed through

FIG. 4. Roentgenograms of chest in Case 2. In *a*, taken immediately before bronchoscopy, note shift of mediastinum to left as evidenced by displacement of trachea. *b*, Taken about twenty-four hours after bronchoscopy, shows mediastinum in normal position with considerable improvement in aeration of left lower lung field.

a period of damaging anoxemia or until the groundwork has been laid for a more serious complication. The following case history, with its accompanying roentgenograms (Fig. 4) and temperature chart (Fig. 5) will serve to illustrate that there are occasions in which plugs in

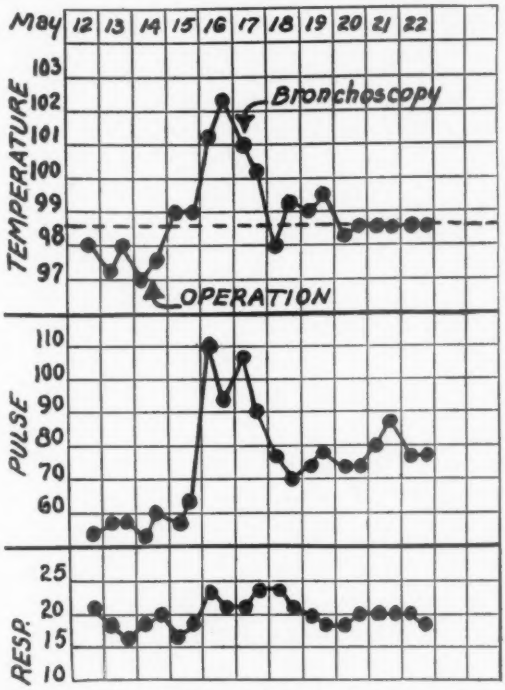

FIG. 5. Temperature chart in Case 2. Note sudden rise in temperature, pulse and respiratory rate, with rapid fall following bronchoscopic aspiration of the air passages.

the air passages resulting in atelectasis of a portion of the lung will not be spontaneously expelled. On the other hand, however, the condition may tend to be progressive in nature.

Case Report 2.—A man, fifty years of age, was submitted to a combined abdomino-perineal resection of the rectum in one stage for carcinoma. His convalescence for the first two days was quite uneventful. On the afternoon of the third postoperative day the patient had a slight chill, following which he had some evidence of respiratory embarrassment. The temperature rose to 101° F., and physical examination at this time showed almost complete absence of breath sounds over the left lower lobe of the lung. In view of the fact that he had had a chill and that it had been more than seventy-two hours since his operation it was thought that his symptoms were very likely due to a pulmonary infection rather than to collapse. Since the symptoms were

thought to be due to true pneumonia and no large amount of fluid was evident in the respiratory passages, bronchoscopy was not performed at this time. During the night the symtoms became progressively worse, with his temperature rising to 102.4° F. A roentgenogram (Fig. 4 *a*) taken at this time showed a complete collapse of the left lung. Bronchoscopic aspiration of the air passages at this time afforded almost immediate relief. A roentgenogram (Fig. 4 *b*) taken the following day showed almost complete re-expansion of the collapsed lung. Following this procedure the patient had no further respiratory difficulties and was discharged from the hospital on the twenty-first day after operation.

We have become convinced that there should be no delay following the diagnosis of collapse of any portion of the lung before active measures are instituted for relief of this condition.

Other patients in whom the incidence and severity of postoperative pulmonary difficulties may be greatly diminished by suction bronchoscopy are those with a suppurative pulmonary disease such as bronchiectasis or lung abscess. This procedure should be carried out immediately preoperatively and as often postoperatively as there is evidence of accumulation of fluid in the air passages which the patient is unable to raise.

Even though these patients may have been treated by postural drainage for long periods of time, the induction of general anesthesia often results in the release into the larger air passages of large quantities of fluid. This release of fluid may be quite early in the induction, before there is sufficient relaxation for an intratracheal tube to be introduced with facility, through which fluid can be aspirated. If facilities are not available immediately for aspirating the fluid which may be suddenly released into the larger air passages it may constitute a real danger to the patient's life as he may actually drown in this fluid. Even if the fluid is not released in amounts large enough to endanger the patient's life from drowning it may result in a spread of the infection. A satisfactory method for managing these patients so as to obviate these hazards may be outlined as follows: (1) The patient is brought to the operating room and under cocaine topical anesthesia a thorough aspiration of the respiratory passages through a bronchoscope is done. (2) The bronchoscope is removed and an intratracheal tube is immediately inserted while the patient is still awake. (3) General anesthesia is now induced with the intratracheal tube in place. Fluid that may accumulate during the course of the operation may be aspirated through the intratracheal tube by means of a urethral catheter. (4) Immediately after the operation is ended, a thorough aspiration of the tracheobronchial tree is again carried out through a bronchoscope, while the patient is still under general anesthesia. As was stated before, these patients, during the course of their convalescence, should be submitted to suction bronchoscopy as often as there is evidence of fluid accumulation which they are unable to raise.

Bronchoscopy has proved to be of tremendous value in the management of postoperative pulmonary complications. This procedure is not a formidable one and is not particularly hazardous even to a patient who is seriously ill. We have never seen an abdominal wound rupture as a result of this procedure. Any patient, regardless of how serious his condition, who has demonstrated his inability to relieve an area of collapse spontaneously or to raise, by coughing, fluids which have collected in the tracheobronchial tree should be submitted to suction bronchoscopy for thorough aspiration of the respiratory passages.

SUMMARY

A brief discussion of some of the factors underlying the development of the more common postoperative pulmonary complications has been presented.

The value of thorough aspiration of the tracheobronchial tree by means of suction bronchoscopy in the prevention and treatment of postoperative pulmonary complications has been discussed.

COMING EXAMINATIONS

AMERICAN BOARD OF ANESTHESIOLOGY: An Affiliate of the American Board of Surgery. *Written.* Part I. Various places throughout the United States and Canada, February 20, 1941. *Oral.* Part II. Saturday and Sunday preceding next Scientific Assembly of the American Medical Association in Cleveland. Applications must be received 60 days prior to examination. Sec., Dr. Paul M. Wood, 745 Fifth Ave., New York.

CHANGES IN THE VELOCITY OF THE BLOOD FLOW DURING SPINAL ANESTHESIA [1]

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THE effects of spinal anesthesia upon the circulation have been the object of numerous investigations. Among these are some controversial studies on the velocity of the blood flow. The circulation time has been determined to show no significant change during spinal anesthesia (1) and to be prolonged as much as sixty per cent. (2). The lack of uniformity in the studies reported and the limited data available for evaluating the results suggested the propriety of further investigation. Furthermore, since the test for circulation time has been used as a diagnostic aid in cases of latent cardiovascular insufficiency (3), it was thought that the determinations might be of value in selecting patients for spinal anesthesia.

In this study, the velocity of the blood flow was determined by a modification of the method of Kohler, who injected a solution of calcium chloride intravenously and noted the time required for a warm sensation to be felt in the mouth, at the perineum and in the hands and feet (4). The solution [2] for testing circulation time contained magnesium sulfate, calcium gluconate, magnesium gluconate, sodium chloride and a small amount of copper sulfate. The salts other than calcium, which is responsible for the warm sensation, are added to minimize possible toxic effects and to preserve the solution. The solution was used directly from the manufacturer's sterile ampoule.

This test is entirely subjective, and, before performing it, the patient must be told exactly what to expect and instructed to report the feeling of warmth at each site immediately. The arm was placed at the level of the heart. A twenty gauge needle was used and the contents of the ampoule (2 cc.) were injected as rapidly as possible into the antecubital vein. A stop-watch was used to time the intervals. The tests were done by two individuals, one injecting and then recording the times reported by the other. No untoward reactions followed any injection, no patient was disturbed by the procedure and no accidents occurred. On infrequent occasions, the first test was not satisfactory because the patient did not understand what he was to do. The test was then repeated after a ten minute interval.

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[2] The Circulation Time Test Solution used in this study was developed by Spier and Wright (5) and supplied under the trade name "Macasol" through the courtesy of the Nepera Chemical Co., Inc., Yonkers, N. Y.

Fifty-eight patients, chosen at random, were used. All but five were males. Physical examinations revealed variations in the status of their cardiovascular systems from normal to generalized arteriosclerosis, to hypertensive, arteriosclerotic and luetic heart disease. Many were ambulatory and none showed evidence of cardiac decompensation. Of the total, twenty-four cases were subjected to lower abdominal, urological or perineal surgical procedures.

Spinal anesthesia was administered by lumbar puncture with a standard technic using procaine hydrochloride (100–150 mgm.), nupercaine (12–14 cc. of 1 : 1500 solution), or intracaine (50–100 mgm.). Except for three patients who received morphine sulphate and scopolamine hydrobromide two hours preoperatively, no preanesthetic medication was given. In all instances, the level of anesthesia was carefully determined by sensory stimulation at intervals throughout the operation. The dermatomes used were those described by Foerster (6). Loss of sensation below the nipple was taken to indicate anesthesia of the posterior roots to T_6, above the nipple to T_5. The blood pressure and pulse rate changes were recorded at five minute intervals. Oxygen, six to ten liters per minute, was given intranasally to a few individuals having nausea, retching or a severe fall in blood pressure.

Throughout this study, ninety-eight tests of circulation time were performed, of which fifty-nine were controls.[3] Twenty-two were performed at approximately twenty-one minutes after the anesthetic drug was injected, six tests were made during spinal anesthesia at least twenty minutes after ephedrine was given and eleven were postanesthetic tests. The exact time after spinal anesthesia was administered, the degree of anesthesia, the blood pressure and the pulse rate were recorded for each patient. The circulation time was determined several hours after the anesthesia had disappeared in the postanesthetic group.

TABLE I

SUMMARY OF CIRCULATION TIME TESTS IN FIFTY-EIGHT (58) PATIENTS

All injections in antecubital vein left arm.

Groups of Cases	Average Circulation Time in Seconds							Sensation Gone
	Throat	Abdomen	Perineum	Hands		Feet		
				Lt.	Rt.	Lt.	Rt.	
Normal Circulation Time..	14.56	19.48	23.00	26.23	25.85	34.43	33.40	79.74
Prolonged Circulation Time	26.28	26.50	40.75	38.71	39.75	49.30	51.5	84.19

Observations on the circulation time in all fifty-eight patients are summarized in Table 1.

[3] This solution for testing circulation time has been used in this clinic without untoward effects in a large number of patients not included in this study.

Sixty-six per cent of these had a normal circulation time; in the others the blood flow was abnormally prolonged. Some of the tests were repeated because of the patient's lack of cooperation. A few were not clear cut and 'blanks' were not unusual. In both the normal and prolonged circulation time, the most consistent determinations were the time from the arm to throat, and to perineum. The least dependable were those from the arm to the abdomen. In the normal group, the variations were in a range that corresponded to that reported with the same method by Kvale and Allen (7). The ages of this group were from 28 to 73 years. Blood pressures varied from normal to a maximum of 240/130. Generalized arteriosclerosis and luetic heart disease were circulatory complications noted. One patient had pyonephritis and another tuberculosis of the kidney.

An abnormal circulation time was found in thirty-four per cent. of the series. The prolongations varied from twenty-five per cent to forty-one per cent. above the normal. Many had no apparent evidence of cardiovascular abnormality. Generalized arteriosclerosis, arteriosclerotic and luetic heart disease were present in others. Most blood pressures were within normal limits but the variation extended from a mild hypotension (98/70) to an hypertension (200/150). There was one patient with bronchial asthma, one with diabetes and another with hydronephrosis.

TABLE II

SUMMARY OF CIRCULATION TIME TEST DURING SPINAL ANESTHESIA

Pre-Spinal* Circulation Time	No. of Cases	During Spinal Anesthesia						Average Per cent. Increase in Circ. Time
		Height of Anes.	Average Circulation Time in Seconds					
			Throat	Abdomen	Perineum	Hand	Foot	
Normal.....	8	Above T-5	28.7	44.5	31.0	53.5	—	47%
	7	Below T-6	16.1	20.2	24.0	28.8	29.0	0
Prolonged...	6	Above T-5	39.3	42.0	—	59.2	—	60%
	3	Below T-6	25.0	44.0	—	40.0	55.0	0

* See Table 1.

Table II summarizes twenty-four observations of circulation time during spinal anesthesia. In this group, fifteen had normal circulation times before the anesthesia and in the remaining nine cases, the times were prolonged.

In the eight cases of the normal group who had sensory anesthesia to a level of T_5 or above, the circulation time was found to be increased by 47.37 per cent. In these the systolic blood pressures fell below the

preanesthetic level. Nausea, retching, perspiration and faintness were other complications. In contrast to these severe manifestations, the seven patients with normal circulation time, whose sensory anesthesia ascended to T_6 or below, had little alteration in circulation time during anesthesia.

Three patients with a normal circulation time, given spinal anesthesia above T_5 and as a result had a greatly prolonged circulation time, then received ephedrine. The prolonged circulation time returned to within the normal range. The blood pressures of these also approached the normal.

Spinal anesthesia to a level of T_5 or above further increased the circulation time by 60.58 per cent. in six patients who had a prolonged circulation time before anesthesia. In three with hypertension, the systolic blood pressures fell more than 100 mm. Hg, but only 28–60 mm. Hg in the others. Here, again, the high anesthesia was accompanied by nausea, retching, perspiration and faintness.

Circulation time was not further prolonged in three patients whose anesthesia reached T_6 or below. In one of these, an hypertensive, the systolic blood pressure dropped 40 mm. Hg, but remained nearly stationary in the others. A determination of circulation time after administration of ephedrine was made in only two patients among those with prolonged preanesthetic circulation times. They were usually in an uncooperative state due to the symptoms associated with the high spinal anesthesia. After ephedrine was administered to one whose originally prolonged circulation time was greatly increased by anesthesia above T_5, the circulation time was improved but did not become normal. One patient did not have a prolonged preanesthetic circulation time changed by spinal anesthesia to T_6. The administration of ephedrine to this individual during anesthesia caused the circulation time to become normal.

In a few instances tests for circulation time performed within one to seventy-six hours after anesthesia had worn off, were found to correspond to the preoperative determinations.

There was noted no correlation between circulation time and the presence of hypertension, or advanced age with its accompanying arteriosclerosis. This confirms the observations of Blumgart and Weiss (3) (8) and Kvale and Allen (7), and leads one to conclude that determinations of circulation time are less satisfactory as diagnostic than as prognostic aids.

It was noted with interest that certain of the determinations made during spinal anesthesia were obtained in anesthetized areas. Although sensory anesthesia was complete in the operated areas the sensations of warmth produced by the test solutions were felt at the site of operation, the perineum, and in the anesthetized lower extremities. Such sensations may transverse sympathetic nerves which enter the cord above the anesthetized area, although they were reported from the

feet by individuals with sensory anesthesia extending to T_5. It should be added that these observations were more often made during spinal anesthesia produced by intracaine and in some cases there was incomplete block of the motor fibers to the lower extremity. It has already been pointed out that spinal anesthesia with intracaine (50–100 mgm.) may not always result in muscular paralysis although sensory anesthesia is complete (9).

The small number of cases studied does not permit a statistical evaluation of postoperative morbidity and mortality in terms of prolonged preoperative circulation time. The studies are being continued with the intention of completing a report which correlates prolonged circulation time with post-spinal anesthesia complications.

The data suggest the value of this test in selecting patients for high spinal anesthesia. Spinal anesthesia above T_6 seriously aggravates an abnormally prolonged circulation time. If spinal anesthesia is to be used for such individuals, and its advisability is seriously questioned, ephedrine should always be used to increase cardiac output and aid in counteracting the ill effects of further decrease in the velocity of blood flow.

The controversy relative to changes in circulation time during spinal anesthesia appears to be accounted for by our data which indicate that the changes depend upon the extent of anesthesia. No significant changes were observed when the level of sensory anesthesia was below T_6. In all but one instance, normal circulation time was increased and prolonged circulation time was further increased when sensory anesthesia was above T_5. The changes in blood pressure and pulse rate that occurred with the anesthesia below the apparent critical level T_5, were not the sole influences on circulation time. With anesthesia at the higher levels there was regularly some accompanying fall in blood pressure and a slowing of the cardiac rate. However, the circulation time was prolonged practically as much in patients with a slight fall in blood pressure as in those with the more pronounced falls in pressure. It was further noted that when sensory anesthesia did not reach T_5 the circulation time was essentially without change in patients with some fall in systolic blood pressure and a decrease in heart rate.

Kvale, et al (7), found an increased speed of blood flow in the extremities after sympathectomy performed for hypertension in twenty-three subjects. The results here with spinal anesthesia below T_6 in ten cases, two with hypertension, were not in complete agreement. Changes in the velocity of blood flow in the lower extremities were within the limits of variation found in these uncontrolled experiments without spinal anesthesia.

The mechanism underlying the increase in circulation time during spinal anesthesia to T_5 or above appears not to be entirely explained. It probably depends largely upon the decrease in cardiac output.

An investigation of the effects of spinal anesthesia upon the circula-

tion in normal man, uncomplicated by medication or surgical manipulation, have strongly suggested that arteriolar dilatation is not responsible for the fall in blood pressure during spinal anesthesia (10). It was pointed out that the diastolic pressure invariably falls less than the systolic and frequently does not fall at all. This fact confirmed in the present study and during other clinical observations does not permit the explanation of hypotension during spinal anesthesia on the basis of vasodilatation. Arteriolar dilatation by reducing peripheral resistance will greatly reduce diastolic pressure if the cardiac output is unchanged. Evidence accumulated in the same study and from other investigations (11) indicate a fall in cardiac output during spinal anesthesia. When sensory anesthesia has not reached beyond T_6 cardiac output may not be greatly altered because a larger area of the body, upper trunk and extremities, head and neck will be available for compensatory constriction as blood pressure falls and heart rate is slowed. Moreover, intercostal paralysis with its effect upon the venous return to the heart has then involved only the lower intercostal muscles. The venous pressure measured directly is decreased with high spinal anesthesia but does not approach the lowest determinations until there is a fall in blood pressure and sensory anesthesia is above T_6 (12). Finally paralysis of cardiac nerves, suggested as an important causative factor in the fall of blood pressure during spinal anesthesia (13), has added significance after the recent experiments of Freeman and Jeffers (14), who found that increasing intracranial pressure produced no changes in arterial blood pressure when cardiac innervation was not intact.

Those patients with a normal circulation time prolonged with spinal anesthesia above T_6, after receiving ephedrine, were found to have again a circulation time within the normal range. Ephedrine which lowers the peripheral resistance raises the systolic pressure by increasing the venous pressure and the cardiac output. Increasing cardiac output removes the primary cause for decreased velocity of blood flow and the circulation time approaches the normal.

SUMMARY

"Circulation Time Test Solution" has been used to study the changes in the velocity of the blood flow during spinal anesthesia. The test is of value in selecting patients for high spinal anesthesia.

Spinal anesthesia, above T_6, greatly increases both a normal or a prolonged preanesthetic circulation time. Sensory anesthesia below this level had little effect upon the velocity of blood flow of either group. Ephedrine is effective in restoring normal circulation time prolonged by high spinal anesthesia.

It is suggested that the changes in circulation time with spinal anesthesia are due principally to a decrease in cardiac output.

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STUDIES ON THE EARLY POSTOPERATIVE REDUCTION OF PROTHROMBIN IN THE JAUNDICED AND BILIARY FISTULA PATIENT WITH SPECIAL REFERENCE TO ANESTHESIA *

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The necessity of vitamin K for the formation of plasma prothrombin is now well established (1). Abundant presumptive evidence now at hand implicates the liver as the site of prothrombin formation (2). Thus at least two factors are necessary for the maintenance of normal plasma prothrombin. One is the adequate absorption of vitamin K or its substitutes (3), and the other is the intact liver mechanism essential for prothrombin production (4). The physiological process by which prothrombin is activated by vitamin K is not clearly understood.

In the course of study of prothrombin deficiency in patients with jaundice, Stewart (5) has shown that a temporary depression of plasma prothrombin frequently occurs during the early postoperative period in these patients. We have observed this same phenomenon. This postoperative fall of prothrombin has in some patients been sufficient to give rise to brisk hemorrhage, and this reduction of prothrombin may occur even though any initial prothrombin deficiency has been corrected by preoperative vitamin K therapy.

The data presented here is a preliminary report concerned with the study of the nature of the postoperative depression of plasma prothrombin and its possible relationship to the anesthetic agent used.

Methods of Study

Two groups of surgical patients were selected for these studies. Group one consisted of patients with normal plasma prothrombin who underwent major surgical operations under various anesthetic agents. Of approximately fifty such patients studied, ten representative of the group are presented here (Table I). Group two (Table II) includes all the patients with prothrombin deficiency who underwent a major surgical procedure during the course of this study. The plasma prothrombin was determined by a modified one-stage technique (6) and the values are expressed in terms of per cent of normal plasma. Prothrombin determinations were made at least once preoperatively and daily postoperatively for four days or longer in each case.

* From the Department of Surgery of The University of Chicago. This work was done in part under a grant from The Douglas Smith Foundation for Medical Research.

TABLE I

PROTHROMBIN STUDIES ON SURGICAL PATIENTS IN WHOM NO PRE-OPERATIVE PROTHROMBIN DEFICIENCY WAS PRESENT

Case No.	Diagnosis	Surgical Procedure	Anesthetic Agent	Total Period of Anesthesia	Postoperative Prothrombin
1	Left frontal lobe tumor	Craniotomy with partial extirpation of tumor	Ether	4 hrs.	No reduction
2	Right mastoiditis	Radical mastoidectomy	Avertin supplemented by ethylene-oxygen	1 hr., 55 min.	"
3	Acute osteomyelitis of skull	Partial osteectomy of skull	Avertin supplemented by ethylene-oxygen	3 hrs., 25 min.	"
4	Carcinoma of stomach	Subtotal gastrectomy	Novocain local with splanchnic block	3 hrs.	"
5	Islet cell tumor of pancreas	Resection of tumor	Nupercaine spinal supplemented by ethylene-oxygen	2 hrs.	"
6	Spinal cord tumor	Laminectomy	Ethylene-oxygen and ether	4 hrs., 45 min.	"
7	Splenomegaly	Splenectomy	Ethylene-oxygen and ether	1 hr., 40 min.	"
8	Carcinoma of breast	Radical mastectomy	Ethylene-oxyxen	1 hr., 50 min.	"
9	Carcinoma of stomach	Total gastrectomy	Novocain local and splanchnic block	2 hrs., 40 min.	Fell to 28 per cent. by 12th day. Given no Vitamin K during this P.O. interval
10	Pulmonary tuberculosis	2nd stage thoracoplasty	Ethylene-oxygen	1 hr.	No reduction

PRESENTATION OF DATA

In Table I is presented a brief description of ten patients selected from group 1. It will be seen that only one patient showed any significant depression of plasma prothrombin during the postoperative period. This patient (case 9), subjected to total gastrectomy, showed no depression of plasma prothrombin during the first four postoperative days. Because of the restricted intake of food by mouth the prothrombin was again determined on the 12th day when it was found to be 28 per cent. of normal. The delay in the postoperative appearance of prothrombin deficiency in this case suggests that this reduction was due to a nutritional insufficiency (7) and not to either the anesthetic agent or the operation *per se*.

In Table II are presented data obtained on seven patients who were

TABLE II

PROTHROMBIN STUDIES ON SURGICAL PATIENTS IN WHOM INITIAL PROTHROMBIN DEFICIENCY WAS PRESENT

Case No.	Diagnosis	Surgical Procedure	Anesthetic Agent	Total Anesthesia Period	Prothrombin Time as Per Cent. Normal		Vitamin K (Naphthoquinone)		PO Days Prothrombin Remained Normal	Remarks
					Initial	Immed. Preop.	Dose /day	Days Given		
1	Stricture of common duct	Laparotomy	Nupercaine 10 cc. spinal supplemented by ethylene-oxygen	1′ 30″	15	100	8 mgm.	5	5	Prothrombin fell to 80 per cent. 6th day, to 40 per cent. 7th day. No food by mouth
2	Common duct stone	Choledocholithotomy and cholecystectomy	Novocain spinal supplemented by ethylene-oxygen	3′ 55″	100	100	8 mgm.	1	1	Prothrombin time dropped to 65 per cent. by 1st P.O. day
3	Common duct stone	Choledocholithotomy and cholecystectomy	Novocain spinal supplemented by ethylene-oxygen	3′ 30″	45	100	8 mgm.	7	7	Developed peritonitis; no food by mouth for 8 days
4	Obstructive jaundice (Carcinoma, head of pancreas)	Cholecystgastrostomy	Nupercaine spinal 14 cc. supplemented by ethylene-oxygen	1′ 30″	75	100	8 mgm.	4	0	No P.O. fall of prothrombin: oral feedings begun 4th day
5	Obstructive jaundice (stricture common duct)	Release of adhesion	Novocain spinal	1′ 20″	80	100	8 mgm.	3	0	No P.O. fall of prothrombin; oral feedings begun 4th day
6	Biliary fistula	Reconstruction of common duct	Ethylene-oxygen	4′ 10″	35	100	8 mgm.	2	1	Prothrombin 80 per cent. normal 1st P.O. day, 50 per cent. 2nd day. Naphthoquinone given
7	Acute hepatitis	Laparotomy with cholecystectomy	Novocain spinal supplemented by ethylene-oxygen	3′ 30″	50	100	6 mgm.	2	1	Prothrombin fell to 65 per cent. by 2nd P.O. day; naphthoquinone then given

found to have initial plasma prothrombin deficiencies. Each of these patients was then given a vitamin K substitute, 2-methyl-1, 4-naphthoquinone, in doses of 2 mgm. with 0.6 gm. bile salts (Lilly) four times daily during their preoperative period. In all of these patients the plasma prothrombins were normal within 36 hours after naphthoquinone therapy was instituted. The naphthoquinone in each case was withheld during the postoperative period until appreciable drops in the plasma prothrombin levels could be demonstrated. During the postoperative period 5 of the 7 patients presented in Table II showed a reduction of plasma prothrombin during their early postoperative periods. Oral feedings which included vitamin K-containing foods were begun on the fourth postoperative day of cases 4 and 5 of this group, and since no reduction of prothrombin was observed by this time, further studies were not carried out on these cases.

COMMENT

From the data in Table I it is obvious that no significant reduction of plasma prothrombin could be demonstrated in the early postoperative periods of patients whose initial preoperative prothrombin concentrations were normal. This observation is supported experimentally by Warner and Rhodes (2) who were unable to effect measurable prothrombin changes in normal dogs subjected to prolonged ether anesthesia or to acute severe blood loss.

However, as shown in Table II, patients who have had an initial prothrombin deficiency, show a postoperative fall, even though the naphthoquinone has been given during the preoperative period with elevation of prothrombin to 100 per cent. It may be that the normal patient has a reserve of potential prothrombin not detectable by this method of determination. This reserve might be made available to the blood stream during the postoperative period thus masking any effect of surgery or anesthesia. The patient with initial prothrombin deficiency, even though treated so that the plasma prothrombin has returned 100 per cent., still might have no reserve. Thus any effect of either the surgical procedure or the anesthetic agent in these patients would be more readily apparent. However, the data in case 9 is suggestive that severe blood loss in itself will not significantly alter the prothrombin level in a patient whose pre-hemorrhagic prothrombin concentration was dangerously reduced. In this case a severe gastrointestinal hemorrhage, occurring six hours after a prothrombin level of 28 per cent. was found, failed to produce any change in the prothrombin concentration within one hour after this episode.

Stewart and Rourke (1) have shown that the postoperative depression of prothrombin may occur in the prothrombin deficient patient treated with vitamin K whose surgery was performed entirely under local novocain anesthesia. Our data, while not permitting a definite conclusion on this point, would seem to support the findings of these

workers. In all but one of our patients described in Table II spinal anesthesia was the primary anesthetic agent employed while ethylene-oxygen was used only in supplementary role, indicating that the prothrombin fall following surgery is not dependent upon the use of a general anesthetic agent.

A prothrombin reading of 100 per cent. indicates that the clotting time of the plasmas of the control and the abnormal are equal. As indicated above this reading does not imply that the quantity of potential prothrombin reserve is equivalent. Since none of these patients presented in Table II received food by mouth during the first four postoperative days it is apparent that the prothrombin levels in these cases must have been maintained by the reserves of potential prothrombin present in the body at time of surgery. It is very interesting then that a close correlation exists between the amount of preoperative naphthoquinone given and the rapidity with which the postoperative falls in prothrombin occurred. Case 3 received 64 mg. of naphthoquinone preoperatively, the prothrombin levels remained normal for seven days after operation; while cases 2, 6 and 7, all receiving less than 20 mgm. preoperatively, developed a significant fall in prothrombin within two days after operation.

The data from these cases would indicate that the early postoperative fall in prothrombin is caused primarily by inadequate administration of vitamin K before operation. It would seem that anesthesia, operative trauma and hemorrhage play no significant role in the production of postoperative prothrombin deficiency.

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THE TREATMENT OF APHONIA BY THE INTRAVENOUS ADMINISTRATION OF PENTOTHAL SODIUM *

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No report on a case of hysterical aphonia successfully treated by the intravenous administration of pentothal sodium has been found in the literature.

Barbiturates were first used in America in psychotherapy by Bleckwenn (1, 2) in 1929. Horsley, (3, 4) in 1936, used pentothal sodium in 2.5 per cent. solution for narco-analysis.

Case report: The patient was a healthy high school girl, with a chief complaint of being unable to talk for three months. The onset was a "cold." Stimulation of neck muscles with an electric vibrator and hypnosis had no effect. The patient became self-conscious and unhappy. There was no family history of hysteria. Past history revealed rheumatic fever with resultant cardiac enlargement and aortic and mitral murmurs. Laryngoscopic examination was negative.

A 2.5 per cent. solution of pentothal sodium was given sufficiently slowly by vein to keep the patient in a hypnotic state. Her response to questions were by lip movements. Occasionally, she uttered a faint sound. Her pharynx was painted with oil of cloves to which she responded with wry facial expressions and tears. At this time, 9 cc. of a 2.5 per cent. solution of pentothal sodium had been injected over a period of 25 minutes. The soles of her feet were then stimulated by scratching. The patient began to kick her feet and protested vocally. In a short time, she answered questions distinctly and slowly but with much effort. The following day, her voice was much stronger. Ten days later, her voice was normal. The patient has maintained her clinical recovery for ten months. Pentothal sodium, in this instance, proved to be a valuable adjunct in the treatment of a psychiatric syndrome.

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EDITORIAL

THE present decade of the short era of surgical anesthesia is an inchoative period. There is no effort to overcome the traditions associated with the practice, but rather a realization that they are extinct. ANESTHESIOLOGY, as a specialty in the practice of medicine, has not adopted the new conception of its practices from its own initiative. Developments have been effected by anesthesia in an effort to keep pace with the progress of the science and art of its patron, surgery. There is a revival of interest in equipping those who will carry the burden of future progress and shoulder the high responsibilities imposed upon surgery. Likewise the progressive surgeon has not been unmindful of the responsibilities that must be borne by those who are designated to perform the accessory services which constitute such a commanding position in the vast array of surgical safeguards. It is for this reason that the newer concept of anesthesiology has become established and that so much insistence has been laid recently upon the preparation of the anesthetist. It is not enough that the surgeon has imposed upon himself a thorough basic scientific preparation to practice adequately his specialty but he is demanding similar preparedness of his associate, the anesthetist. Today the anesthetist is expected to qualify for a much more important role in surgical therapy than has been heretofore demanded. It is no longer sufficient unto the needs of surgery that the anesthetist practice merely his art and present the surgeon with a patient insensitive to pain and with relaxed musculature. It is expedient that his qualifications include knowledge that fits him to become for one thing the pharmacological and biochemical consultant of the surgical team. Aside from knowing the pharmacologic and physiologic action of anesthetic drugs, as well as those used to counteract them, the anesthetist's interests include blood transfusion, intravenous therapy, oxygen therapy, therapeutic nerve blocking and resuscitation.

The specialty of anesthesia is finally becoming interpenetrated with the scientific attitude. This attitude, joined with resolute conviction, will be an answer to its problems. There is a definite return to the truly scientific tradition and an alignment that gives it a form consistent with modern science. The anesthetists have accepted the challenge imposed with the new order of anesthesia. One of the first significant steps to be taken was the reorganization of the New York Society of Anesthetists on a national rather than a local basis. The new organization was named The American Society of Anesthetists, Inc. This national society, cooperating with the Section on Surgery, General and Abdominal, of the American Medical Association, and with the American Society of Regional Anesthesia, Inc., sponsored the for-

mation of the American Board of Anesthesiology, Inc., an affiliate of the American Board of Surgery, Inc. This Board, with the benevolent guidance of members of the Surgical Board, has functioned since 1938. An effort to achieve objectives, as outlined by the Advisory Council for Medical Specialties, has been made. As a further effort, the latest project is represented in this venture, the launching of a new journal, "Anesthesiology." The keynote is progress. The watchword is education.

As knowledge accumulates in any field of endeavor the related literature increases in volume. The medical sciences are no exception. The enormous amount of medical literature coming from the presses today is an indication of the recent rapid advances in medical practices. It is inconceivable that the medical and related professions would accumulate knowledge without immediately disseminating it. There is no convenient method for so doing other than the recognized medium of exchange, contemporary medical literature. Although it is a fact that the number of medical periodicals published annually have reached a staggering figure, it is equally true that medical discoveries and learned discussions are available in greater abundance.

There is considerable agitation from many sources to curtail the output of medical literature and many of the arguments used as a basis for demanding such action are sound. The proper procedure for exercising control over the increasing stream of publications is a more complex proposition. It would seem logical to assume that much could be accomplished by the more careful selection of the material to be published. If articles are judged solely upon their merits and only those published which contain original work, comprehensive merited reviews or report valuable experiences, the bulk of medical literature would be decreased as rapidly as it has grown. Articles published because the author has gained a reputation from other work or by virtue of position, and those published because they happen to have been presented before some medical society frequently need strict editing. There should be an insistence upon brevity in the process of editing. If all but the essential facts in articles were omitted many of them would have nothing left and practically all of them would be much shorter.

The American Society of Anesthetists, Inc. are convinced that in their special branch of medicine there is a definite need and place for ANESTHESIOLOGY. However, they realize the responsibility that is theirs; namely, to avoid further burdening the medical literature with articles that do not merit publication.

BOOK REVIEWS

Shock—Blood Studies as a Guide to Therapy. JOHN SCUDDER, M.D., Med.Sc.D., F.A.C.S. 315 pages, 55 illustrations and 5 plates. J. B. Lippincott Company. Price, $5.50.

Shock is a pathological physical state which occurs commonly in a variety of conditions. These conditions embrace most branches of medicine and make it important that physicians and surgeons have an understanding of shock which will allow them to diagnose and treat it rationally.

This new book by John Scudder is divided into four parts, namely: one, historical and experimental; two, varieties of shock, analysis and treatment; three, historical development and bibliography; and four, laboratory manual.

Allen O. Whipple in the foreword of the book tells us that John Scudder while working in the United States in 1815 investigated fluid balance as a thesis for his degree of doctor of medicine. Later he worked in India where he saw much of dehydration in cholera and dysentery. Three generations later we find the present John Scudder in India interested in dehydration. His experience there was transferred to the treatment of intestinal obstruction and shock where equal success seemed to be obtained with the proper use of solution of sodium chloride. Dr. Scudder began working in this country on the problem of dehydration as found in intestinal obstruction and fistulae. This led to the estimation and treatment of the dehydrated state in the presence of burns, acute pancreatitis and perforated ulcers of the gastro-intestinal tract. This work was carried on in the Rockefeller Institute for Medical Research where, in addition, associated work was done on plasma proteins and the preservation of human blood.

Part one: The historical references to shock date back to early in the eighteenth century when a French surgeon and an English minister made accurate observations, the validity of which it has taken two centuries to substantiate. The word shock first appeared in 1743 and was associated early with trauma. Generalized vaso-constriction was observed in shock, affecting both veins and arteries, following which there was a decrease in volume flow. Venous pressure increases, capillary congestion and dilatation occur and the result is an increase in the capillary bed. The theories of shock include: one, toxemia; two, loss of circulating fluid; three, neurogenic imbalance; and four, adrenal exhaustion. All of these theories have been under investigation during the past two hundred years.

Historically, the treatment of shock called for heat, intravenous fluids (hypertonic and normal saline, gum acacia, and sodium bicarbonate) emetics and lavage, sedation, Trendelenberg position, oxygen, and transfusions. The latter was advocated as long ago as 1750. In recent years preserved blood has been utilized, also preserved plasma.

In the experimental work with traumatic shock the electrolytes were considered. Among the anions, chlorides have been found both increased and decreased, bicarbonates are often reduced, and proteins are generally decreased. Among the cations, sodium is decreased, calcium may be increased or decreased, while potassium is increased. The non-protein-nitrogen,

blood urea, and creatinine are increased, the blood sugar fluctuates, and the hydrogen ion concentration is increased.

Potassium is found in both animal and vegetable cells. A phenomenon which is generally known is that potassium accumulates in cells living in a medium richer in sodium than potassium. Potassium acts first as a stimulant then as a depressant to both the central nervous system and peripheral nerves. It is a poison to striated and smooth muscle. On cardiac muscle, in small amounts it slows the rhythm and lengthens the refractory phase, while in larger amounts it causes cardiac arrest. Striated muscle contains a predominance of potassium, three to one over sodium, and this potassium is easily lost after trauma, thus its importance in the conception of traumatic shock. On blood vessels potassium causes vasoconstriction, acting locally upon the muscle in the vessel wall as well as by increasing irritability of nerves supplying the vessels. Even when present in small amounts potassium causes a fall in blood pressure. Assimilation takes place through the gastro-intestinal tract and excretion is through the kidneys chiefly. The level of potassium in the body is maintained by efficient kidney excretion, holding back by the liver, excretion into bile, temporary storage in muscle and red blood cells, and loss by salivation or vomiting. Thus in shock whether caused by tissue abuse, loss of fluids, hemorrhage, stimulation of the sympathetic nervous system, injection of toxins or destruction of adrenal tissue there is an alteration of potassium metabolism, a derangement which serves as an indication of profound injury of cells.

The physical measures of hemo-concentration that are of value in shock are: specific gravity of peripheral blood and venous blood, cell count and cell volume, determinations of plasma proteins and potassium. The specific gravity of blood is found to change in shock several hours before the change in pulse and blood pressure. In 1884 Roy gave a method of measuring shock (specific gravity of blood) more delicate and of more value than determination of blood pressure. In 1926 Hamilton and Barbour introduced the falling drop method of determining the specific gravity of body fluids; this method is twenty-five times more sensitive than the average red blood cell count in measuring dehydration. Briefly the specific gravity of peripheral blood, the red cell count, cell volume, and plasma potassium all are increased in hemoconcentration.

Part two. This part of the book contains rather complete case studies and analysis of various types of shock, namely: postoperative, traumatic, traumatic complicated by hemorrhage, hemorrhagic, burns, perforated duodenal ulcer, and primary shock due to paraganglioma of adrenal tissue. Normal values are given as obtained from healthy adult males. The treatment of shock is presented in detail and the results are shown graphically.

The treatment presented consisted of transfusions, administration of oxygen, external heat, 5 per cent sodium chloride as well as normal saline, Ringers solution, saline with glucose, and cortical extract. The more severe the shock, the higher were the values for potassium in the plasma and, as such it could be used as a prognostic aid. If the plasma potassium was increased over one hundred percent the outcome was fatal, whereas seventy one per cent. of patients recovered in whom the increase was fifty per cent. or less. Several interesting studies are presented concerning five patients who suffered severe burns in the Hindenburg disaster. They presented the most striking changes in both peripheral and

venous blood with a high specific gravity, high cell volume, increased plasma potassium, and decreased plasma proteins.

The author feels that hypertonic saline is to be used only in small amounts (200–500 cc.) and its effects should be controlled by repeated blood determinations as well as by the response of the patient. The best success was obtained with the combined administration of hypertonic sodium chloride, cortical extract and transfusions.

Cortical extract is discussed at length and its use is advocated in treatment of shock as it is said to correct many altered physiological functions and abnormal chemical and physico-chemical states. It acts to restore blood volume, relieves hemo-concentration, raises blood pressure, and increases alkaline reserve through promotion of base retention. It restores renal function, causing increased excretion of potassium as well as ammonia and retention of both sodium and chloride. It increases heat production, decreases the retained nitrogenous elements in the blood and lowers the value for blood potassium. Cortical extract, where used, showed a better survival rate (52 percent) in moribund patients and in several cases of post-operative shock, where the usual measures failed; it alleviated the shock when administered with salt solution. The extract is given intravenously in repeated small doses.

The author does not say that shock is due to potassium poisoning but believes that alterations in potassium in both blood and body fluids serve as a measure of profound cellular changes.

Part three of the book is unique in that it is concerned entirely with historical developments in the conception and treatment of shock, in the physiologic and toxicologic effects of potassium, and of some of the functions of the adrenal glands.

An extensive bibliography is provided, citing over five hundred references.

Part four is a short laboratory manual describing the technique of the different determinations suggested by the author.

Summary: This book contains material suitable for wide clinical application in daily practice. It is well written and is excellently authenticated by references. Dr. Scudder has studied his problem profoundly and has given us a foundation for clinical practices that may be responsible for the saving of many lives.

C. B. H.
R. M. T.

Cyclopropane Anesthesia. Benjamin Howard Robbins, B.A., M.S., M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine. Pages 175. Baltimore: Williams & Wilkins Company, 1940. Cloth—Price $3.00.

This small but comprehensive book serves to clarify the present status of cyclopropane as an anesthetic agent. Starting from the history of its first discovery and dealing with its physical and chemical characteristics and methods of manufacture, it then devotes a series of chapters to the effects of cyclopropane on the important organs and tissues of the body, both in the experimental animal and the human subject. These chapters contain useful summaries. The figures and tables which are presented are illustrative and easily read. One of the eleven chapters in the book is devoted to the clinical administration of cyclopropane as an anesthetic agent and while several techniques are mentioned there is a limited amount of discussion regarding actual clinical administration. Separate chapters discuss the complications following cyclopropane anesthesia and the indications and contraindications for the use of this valuable anesthetic

agent. The last chapter is devoted to the explosive hazards and mentions the common precautions that may be taken but no mention is made of any new device that is known to give adequate protection against static accumulations. There is a fairly comprehensive bibliography and an adequate index. The chapters dealing with the chemical and physical properties are quite technical, and the clinical anesthetist might feel that more space could have been devoted to the problems involved in administration of the gas. The author suggests the interesting point that cardiac irregularities so often encountered in cyclopropane anesthesia might be eliminated by using barbiturates, in place of, and to the exclusion of, morphine as premedicating agents. The book should prove of value to both anesthetists and pharmacologists.

J. T. T.
R. M. T.

The Evolution of Obstetric Analgesia. ANDREW M. CLAYE, M.D., (Leeds), F.R.C.S. (Eng.), F.C.O.G., Leeds, Eng., Professor of Obstetrics and Gynecology, University of Leeds; Honorary Surgeon, Leeds Maternity Hospital, and Hospital for Women; with a chapter by W. STANLEY SYKES, M.A., M.B., B.Ch. (Cantab.), D.A., Leeds, Honorary Anesthetist, General Infirmary, and Hospital for Women. Oxford University Press. London, 1939, 99 pp.

The author's purpose in presenting this small volume is to fill the need of a book in English stressing the historical aspect of obstetric analgesia. The writer emphasizes two of the highlights of the subject; the introduction of ether and chloroform, and the development of twilight sleep.

The first chapter is devoted to ether and chloroform, which is a concise and reverential summary of their introduction by Sir James Y. Simpson. The contributions of a number of other workers are sketched but the subject is not completely covered. The controversies and oppositions—lay, clerical, and medical—incident to the introduction of the new methods in childbirth are briefly mentioned.

The second chapter passes abruptly into the development of twilight sleep without mention of preceding advancements. Two pioneers are briefly mentioned with a summary of their methods and results. Gauss, who worked at Freiburg, has received a disproportionate amount of space. The subject matter is largely devoted to detailing the modifications of dosage of morphine and scopolamine and enumerating the criteria and tests used in evaluating the success of the amnesia. The adverse effects are minimized. Results are quoted without analysis or comment. The controversies subsequent to the introduction of twilight sleep are omitted.

The gaseous anesthetics are grouped together in one chapter. The dangers of asphyxia associated with nitrous oxide are under-emphasized. The chapter is burdened by the detailed descriptions of various types of apparatus for administering nitrous oxide and the results of various investigators using these machines. The risk of explosion with ethylene is emphasized. The discussion of cyclopropane is inadequate since it consists only of a description of a single case of the author.

The large and important subject of the barbiturates is dismissed with a description of the author's use of nembutal and pernocton, and his clinical impressions of them.

The book is merely of casual interest to anesthetists because of its sketchy presentation and superficial discussions.

R. J. F.

ABSTRACTS

Editorial Comment: A fixed style of presentation for this department of ANESTHESIOLOGY has purposely not been defined. It is the wish of the Editorial Board to provide our readers with the type of abstract they desire. Correspondence is invited offering suggestions in regard to the length of abstracts, character of them, and source of them.

H. R. HATHAWAY. *The Use of Cyclopropane in the Wisconsin General Hospital During the Past Year.* South. M. J. 33: 45–50 (January), 1940.

"As local conditions definitely determine the anesthesia practices in a given situation, any inference or suggestion that cyclopropane ought to be used in all clinics in the manner to be described is far from the writer's thoughts. . . . The following data are partially based on the annual report of the anesthesia department of the Wisconsin General Hospital for the year 1938. As ten months have elapsed since this material was compiled, various changes have been made in the use of cyclopropane. . . . During 1938, out of 4668 anesthetic administrations conducted by the department, slightly less than 50 per cent. were done with cyclopropane. This is within 0.5 per cent. of the previous two years and will apparently hold for the present year. This agent was employed in 59 per cent. of the instances where inhalation anesthesia was used. This percentage also compared within 0.5 per cent. of the previous two years. It suffices to say that this agent has been and is still being used for all types of surgical procedures. Whereas we definitely feel that there are extremely few absolute indications or contraindications for the choice of any anesthetic agent or technic, provided the administrator is capable and knows what he is about, there are certain advantages and certain limitations which make for a wise choice. Some of these will be mentioned in the case of cyclopropane.

SURGICAL PROCEDURES

"*Intracranial.*—Of 59 operations in this group, only 3 were done with cyclopropane, while 25 were done with ether, and 28 were accomplished with either nitrous oxide or avertin with amylene hydrate, or a combination of the two. Since January, 1939, we have favored the last named combination largely because of the absence of fire hazard (the electro-surgical unit is used with few exceptions in these operations).

"*Neck.*—This group includes operations on the thyroid gland, removal of cysts and lymph nodes, tracheotomy, cervical sympathectomy, etc. Of 138 surgical procedures on the thyroid gland, only 13 were done with cyclopropane while in 107 instances, nitrous oxide was used. This was due to the fact that we prefer to use an inhalation anesthetic agent and still keep the laryngeal reflex active. . . . Of the remaining 36 procedures in this group, 19 were done with cyclopropane.

"*Head, and Ear, Nose and Throat.*—This group includes plastic operations on the scalp, face, nose, lip, palate, jaw, and tongue, intranasal surgery, mastoidectomy, tonsillectomy and adenoidectomy, bronchoscopy, esophagoscopy and gastroscopy. Of the 376 surgical procedures, 295 were done with ether while cyclopropane was used for only 28. . . . Bleeding or oozing is difficult

to control without the use of some local vasoconstricting agent. Epinephrine is most commonly used for this purpose in our clinic. According to recent laboratory investigations when a sympathomimetic amine will possibly be employed during the course of an operation which requires the use of a potent inhalation agent, ether is the wisest choice.

"*Dental.*—The vast majority of dental surgery is accomplished by procaine infiltration or block anesthesia. Inhalation anesthesia by the endotracheal technic is used for all major dental operations such as complete extractions, removal of multiple impacted molars, and wiring of fractured jaws. In 48 instances, cyclopropane was used, while ether was used in 33.

"*Eye.*—Many operations upon the eye are performed under instillation or infiltration anesthesia. . . .

"*Perineum.*—This group includes not only operations on the structures in this region, but also those that are accomplished by the perineal route. Of 1,274 procedures, 686 were done with cyclopropane, 44 with ether, 177 with nitrous oxide, 201 with procaine spinal analgesia, and 67 with procaine transsacral block. The majority of anal operations were done with procaine transsacral block, as it allows for complete sphincteric relaxation, thus facilitating the operation. Of 276 transurethral prostatic, cystoscopic or bladder procedures, only 12 were done with cyclopropane, while in 189 instances, low procaine spinal analgesia was used. This choice (low spinal) is made wherever feasible in these operations because of the elimination of the fire hazard. Of 629 vaginal outlet operations, such as dilatation of the cervix and uterine curettage, perineal repair, vaginal hysterectomy, and endometrial biopsy, 531 or 84 per cent. were done with cyclopropane. In practically all obstetrical cases, such as spontaneous or forceps deliveries, nitrous oxide is used. In those instances when satisfactory analgesia or anesthesia is not possible without oxygen lack, as when the infant's head passes over the perineum or when more relaxation is required, cyclopropane is added as a supplemental agent. In 1936, such supplementation was necessary in 66 out of 163 instances.

"*Inguinal.*—This group is composed largely of operations for hernia. . . . In 50 per cent. of the instances, cyclopropane was administered.

"*Extremities.*—This group includes operations on the bones, joints, muscles, tendons and nerves, as well as amputations and reduction of fractures. Cyclopropane was used in 70 per cent. of 834 surgical procedures in this classification.

"*Spinal Cord and Column.*—In 69 surgical procedures in this region, such as laminectomy, spinal fusion, etc., cyclopropane was used in 45 instances.

"*Thorax.*—This group includes breast operations as well as those on the bony thoracic cage and pleura. It also includes intrapleural surgical procedures. In the majority of operations on the breast, nitrous oxide was used as here again no muscular relaxation is necessary. However, in 16 instances out of 79, cyclopropane was employed. In all but 32 of 211 thoracic operations, both extra- and intra-pleural, cyclopropane was used. In only 9 of the 32 instances where it was not employed was nitrous oxide used. Ether was used for two complete pneumonectomies. In this group there was only one operation on the heart, and cyclopropane was the anesthetic agent in this instance. . . .

"*Intraperitoneal, Upper.* — This group includes such surgical procedures as ventral hernia repair, exploratory celiotomy with or without lysis of adhesions, cholecystectomy and operations on the bile ducts, splenectomy and operations on the stomach. In a total of

258 operations, cyclopropane was used 58 times, ether 181, and procaine spinal analgesia on only 7 occasions. In the majority of the 58 operations which were completed under cyclopropane anesthesia, controlled respiration as described by Waters was utilized. Ether was chosen as the anesthetic agent for splenectomy because of the findings of Searles.

"*Intraperitoneal, Lower.*—In this classification are included appendectomy, intestinal operations, exploratory celiotomy, various gynecologic pelvic operations and cesarean section. Cyclopropane was the anesthetic agent in two-thirds of the 692 operations in this region. Ether was used in 26 per cent. and here again procaine spinal analgesia was used only 7 times. Cyclopropane was successfully employed in cesarean sections, 29 in number.

"*Abdomen and Lumbar, Extraperitoneal.*—Into this classification fall the operations on the kidney, ureters and urinary bladder. In 75 per cent. of these 90 procedures, cyclopropane was used.

PATIENT'S AGE AND PHYSICAL STATE

"Cyclopropane was employed in only 7 out of 72 operations on infants under one year of age. It was used in 18 per cent. of the 454 surgical procedures on children from 1 to 9 years. There was an even distribution as compared with other anesthetic agents throughout the remaining age groups.

PREMEDICATION

"Morphine and scopolamine alone in the ratio of 25 to 1 given subcutaneously one hour and a half before operation was used as premedication in 87 per cent. of all cyclopropane administrations. Moderately small doses were used throughout. Barbiturates were rarely used.

TECHNIC

"The 'to and fro' carbon dioxide absorption technic is used for over 90 per cent. of all cyclopropane administrations. . . . At the end of anesthesia, active pulmonary ventilation is produced so as not to leave rapidly absorbable gases in the alveolar spaces. This is best accomplished by having the patient take a few deep breaths of air. If he is still unconscious and not breathing actively, the lungs are inflated with air by use of the mask and breathing bag or by dribbling just enough pure carbon dioxide over his nose to cause active ventilation. In view of the present interest in the fire and explosion hazard it is well to state that the patient, operating table and anesthetic machine are all contacted by the anesthetist immediately before the administration of any anesthetic. This is done to equalize any static electrical charges that may have accumulated. Furthermore, as an additional precaution the cyclopropane is not turned on until after the mask has been adjusted to the patient's face." Bibliography—10 references.

J. C. M. C.

L. H. MOUSEL. *An Unusual Case of Convulsions under Anesthesia.* Proc. Staff Meet., Mayo Clin. 15: 33–36 (January 17), 1940.

"Convulsions during general anesthesia have been reported in the literature with increasing frequency during the last twelve years. Many of these convulsions have terminated fatally. It seems opportune to present this case in order that renewed interest might be created in the subject of so-called ether convulsions and to stress the importance of being on the alert for such a condition. Early recognition and treatment are imperative. . . .

"A child, six years of age, was first operated on for lymphedema on April

4, 1939. Nitrous oxide, oxygen and ether were administered at that time. Anesthesia and convalescence were uneventful. A skin graft was done on August 7, and a plastic operation was done on August 21, 1939. Nitrous oxide, oxygen and ether were administered for both procedures. Anesthesia was uneventful.

"The child was admitted for preparation for another operation on November 4, 1939. Twenty-four hours before operation, the body temperature was 99.6° F. (37.6° C.) and the pulse was 104 beats per minute. On November 6, 1939, a plastic operation was carried out under nitrous oxide, oxygen and ether anesthesia. The course during the operation was not unusual. At the conclusion of the operation, after anesthesia became light, muscular twitchings were noticed first around the eyes. The twitchings rapidly spread to the face, neck and trunk. Convulsions soon became severe. The pulse became rapid, the pupils dilated and severe cyanosis developed. Six or 7 cc. of a 2.5 per cent. solution of pentothal sodium were injected intravenously and a high concentration of oxygen was administered. The convulsions ceased almost immediately and the cyanosis soon disappeared. There was evidence of mucus in the trachea. Tracheal and bronchial aspiration was carried out by means of suction through a catheter.

"The child was returned to her room and placed in an oxygen tent. One hour after the operation, her body temperature was 101.4° F. (38.6° C.) and the pulse rate was 160 beats per minute. On the following day, her temperature was normal and convalescence was uneventful.

"The concentration of blood calcium immediately following the convulsion was 9.5 mg. per 100 cc. Cultures made from nasal pharyngeal swabbings showed growth of a neurotropic strain of streptococcus.

"Two weeks following the convulsions, another operation was carried out under similar circumstances. The same anesthetic agents were used. Anesthesia and recovery were uneventful. Nasal pharyngeal swabbings taken at this time did not contain streptococci. Cultures taken from the lymphedematous tissue removed showed the presence of *Staphylococcus aureus*. . . .

"It seems that this case adds to the evidence of the neurotoxin hypothesis as presented by Rosenow and Tovell. This child had three previous anesthetizations with nitrous oxide, oxygen and ether, with nothing unusual happening during anesthesia. Cultures of the throat were not taken following the first three anesthetizations. The fourth anesthetization produced a convulsion. Streptococcus was cultured from her throat at that time. A fifth anesthetization, two weeks following the convulsion, was uneventful and growth of streptococci was not obtained from cultures of her throat at that time." Bibliography—15 references.

J. C. M. C.

E. M. HEDIGER, M. B. CHENOWETH AND H. GOLD. *The Use of Bulk Ether in Surgical Anesthesia. The Stability of Ether in Cork-stoppered Metal Containers.* J. Am. Med. Assoc. 114: 1424–1428 (April 13), 1940.

The authors reaffirm the conclusions reached in their previous studies. Hospitals may use ether in bulk for anesthetic purposes. This ether can be transferred from a 25-pound drum, either directly by a funnel or by a copper siphon arrangement, to small emptied anesthetic cans which can then be stoppered with cork. Such ether in a drum can be kept for at least a month without developing impurities. Where less ether is used, the small quarter pound tins can be filled from 5-pound cans instead of 25-pound drums. A saving in the cost of ether can be effected. This practice involves no com-

promise with the purity of the ether or the safety of the patient. Bibliography—14 references.

A. S.

E. V. ALLEN AND E. B. TUOHY. *Relief of Somatic Pain by Local Anesthetization.* Proc. Staff Meet., Mayo Clin. 15: 58–60 (January 24), 1940.

"A common and distressing complaint by patients is pain affecting various somatic structures such as those of the abdomen, chest, cervical and occipital regions and of the lumbosacral regions. . . . It is not the purpose of this presentation to discuss mechanisms of somatic pains or the frequently complicated genesis of them but to reemphasize observations by other that such pains may be relieved frequently by local anesthetization. Naturally, such injections are not to be given indiscriminately and not until extensive attempts have been made to find a cause for the pain for which there may be more specific therapeutic measures. Previous investigators have emphasized that painful shoulder, painful knee, talalgia, sacro-iliac pain, herpes zoster, neuralgia, arthritis of the spinal column, sciatica, myositis, fibrositis and psychalgia may be relieved by local anesthetization of painful regions, by paravertebral nerve block or by injection of an anesthetic agent into a nerve. A recent report states that ninety-eight of 134 patients (73.1 per cent.) were completely or largely relieved by such procedures as brachial plexus block, injection into bursae, paravertebral block, injection of sciatic nerve, local infiltration or by injection into or around joints. Relief may be transient, in which case injections are repeated at intervals of three to twenty-one days as often as ten or twelve times. When injections are repeated there is evidence of prolonged relief. In many instances an oily solution of the anesthetic, to prolong action, is more efficacious than an aqueous solution. Pleural pain may be relieved by deep injection of procaine. It is easy to understand why local anesthetization of a painful area produces temporary relief from pain. It is difficult to understand why temporary anesthetization may produce permanent relief from pain. . . .

"We wish to emphasize that local anesthetization is no cure-all for somatic pain. The procedure should never be substituted for an extensive attempt to discover the cause of pain and never be performed unless such an attempt has been made. When used cautiously, local anesthetization has been, in our experience, a useful therapeutic measure." Bibliography—3 references.

J. C. M. C.

G. H. A. CLOWES, A. K. KELTCH and M. E. KRAHL. *Extracellular and Intracellular Hydrogen Ion Concentration in Relation to Anesthetic Effects of Barbituric Acid Derivatives.* J. Biol. Chem. 68: 312–329 (March), 1940.

For each of two representative barbituric acids investigated it is found that the extracellular concentration of undissociated molecules required to produce a 50 per cent. reduction in the rate of cell division of fertilized Arbacia eggs is not affected by a decrease in the intracellular pH. For each of three representative barbituric acids investigated it is found that the extracellular concentration of undissociated molecules required to produce a 50 per cent. reduction in the rate of cell division is also not affected by an increase in the intracellular pH. These observations indicate that it is the barbituric acid molecule and not the barbiturate anion which is active inside the cell in producing the anesthetic effect; thus, the barbiturates are to be classified with non-ionizable anesthetics like the ethers

and alcohols in respect to their mechanism of action.

A. S.

W. J. MEEK. *Effects of the General Anesthetics and Sympathomimetic Amines on Cardiac Automaticity.* Proc. Staff Meet., Mayo Clin. 15: 237–240 (April 10), 1940.

"In the use of cyclopropane for general anesthesia it has been observed that cardiac arrhythmia sometimes develops if the concentration of the gas is great. In experiments on dogs it was found that an animal could be held in deep surgical anesthesia for hours by means of cyclopropane without any demonstrable arrhythmia. However, irregularities began to appear about the time of respiratory arrest when the concentration of the gas averaged 39.4 per cent.

"Under artificial respiration animals could withstand about 46 per cent. of cyclopropane before cardiac irregularities appeared. If, when the irregularities came on in a spontaneously breathing animal, the respiratory exchange was increased by artificial respiration there was usually rapid recovery. If the irregularities appeared after a respiratory standstill, artificial respiration with oxygen usually brought about a prompt revival.

"These facts all indicate that anoxemia is a predisposing condition for arrhythmia but it is equally clear that the gas itself is toxic in heavy concentrations. If artificial respiration is instituted with cyclopropane in pure oxygen, the gas can be crowded to about 60 per cent. without difficulties. At about this point, however, the heart becomes paralyzed in spite of the alveolar oxygen being considerably greater than normal.

"Premature beats and independent rhythms arising below the sino-auricular node are due to one of two conditions or to some combination of the two. In the first place, if the sino-auricular node is depressed in its rate of discharge, some lower automatic center may accumulate enough irritable material to bring about impulse formation which is recognized as an extrasystole. The lower automatic region may continue to rebuild its automatic material faster than the depressed sino-auricular node, in which case there is some kind of an ectopic rhythm, either nodal or ventricular. Since automaticity decreases as we descend from the auriculoventricular node, these rhythms are slow and they always depend on a reduction in activity of the sino-auricular pacemaker. Since vagal innervation also decreases downward in the heart, the arrhythmias mentioned may all be brought about by vagal stimulation, which depresses the sinus out of proportion to other parts. Such irregularities are known as escape phenomena.

"In the second place premature beats and independent rhythms arising below the sino-auricular node may appear because of actual stimulation of the lower automatic centers by which their irritability is raised above that of the supraventricular regions. It may be difficult to say which of the two conditions is responsible for an occasional extrasystole, but when the ventricular rhythms are fast enough to supersede the sinus rate there is little doubt that ventricular ectopic centers have been stimulated. Ventricular tachycardia of 300 per minute may arise in the dog's heart in this way. Not only do such rhythms quickly reduce cardiac output but they also frequently grade over into ventricular fibrillation.

"Since cyclopropane anesthesia when pushed to respiratory arrest resulted in extrasystoles and frequent tachycardia, it was concluded that this agent exerts a strong stimulation on the automatic ventricular mechanisms.

"The work of Kurtz, Bennett and Shapiro demonstrated that cardiac ir-

regularities during anesthesia with cyclopropane, chloroform or ether, are more common in clinical practical than is generally supposed and that clinical experience is not essentially different from that already related for animals.

"In our experiments, in order to find the effect of anesthesia on the automatic mechanisms, adrenalin was injected. This drug is known to stimulate not only the sino-auricular node but also the specialized tissue in the ventricle. The basis of our method for determining the effect of an anesthetic on automatic activity is simply to find a dose of adrenalin which in the normal animal will produce only reflex inhibition of the sinus, with or without escape of the auriculoventricular node, bundle or ventricular tissue, but which is not strong enough to bring any part of the heart into the showers of extrasystoles, tachycardia or fibrillation. If the same dose given under anesthesia results in either fast sino-auricular or ectopic rhythms the indication is that the anesthetic has made the automatic tissue more irritable. The part concerned can be more or less localized by the type of irregularity.

"Our experiments lead to a number of interesting conclusions:

"1. The stimulating or sensitizing effect on the automatic tissue of the dog's heart for the three gaseous anesthetics studied increases in the following order: ether, chloroform and cyclopropane.

"2. In ether anesthesia auriculoventricular rhythm is common after the injection of adrenalin. Under the same conditions chloroform favors ventricular extrasystoles, nodal and ventricular rhythms and occasionally ventricular tachycardia. Ventricular fibrillation did not occur in our experiments with our standard test dose of adrenalin. It could of course have been brought out with heavier doses. Cyclopropane favors ventricular extrasystoles, fast ventricular rhythms or tachycardia and occasional ventricular fibrillation.

"3. Our experiments do not justify the common belief that chloroform acts on all mammalian hearts as it does on the heart of the cat. The dog may be carried to respiratory arrest with the production only of slow nodal and ventricular rhythms. These may continue to death without fibrillation.

"4. In the dog the increased irritability of the automatic tissue to chloroform and cyclopropane is directly related to the concentration of the anesthetic agent.

"5. The use of adrenalin is strongly contraindicated in cyclopropane anesthesia. Not only is this clearly demonstrated for the dog but there is also good reason for believing it is equally true for man. At least one case has been reported in which an injection of adrenalin was promptly followed by cardiac delirium and death.

"Since cyclopropane so specifically sensitized the heart to adrenalin, it was decided to investigate the effect of other blood pressure raising amines under the three anesthetic agents already studied.

"Ephedrine in thirteen controls gave the expected escape phenomena due to high blood pressure. There was but one tachycardia which lasted for only two seconds. Under cyclopropane there were two tachycardia and in all cases the sinus rate spoke for some ventricular stimulation although ventricular dominance was not often attained.

"Cyclopropane does not particularly sensitize the ventricule to propadrine or amphetamine (benzedrine), as is shown by the absence of ventricular tachycardia. It appeared only once for amphetamine and not at all for propadrine. Both drugs, however, like ephedrine, drove the sinus into tachycardia. This of course may have masked some ventricular stimulation.

"Cobefrin, kephrine and epinine were much alike. Cyclopropane enabled all three to bring out ventricular tachycardia in every experiment. Epinine and kephrine increased the

sinus rate greatly, cobefrin somewhat less.

"Although paredrine produced but one ventricular tachycardia it accelerated the sinus greatly in all cases.

"Arterenol showed a selective action on the ventricle sufficient to cause tachycardia even with evidence of simultaneous sinus stimulation.

"Although synephrin did not stimulate the ventricle it did raise the sinus rate to the stage of tachycardia.

"Neosynephrin produced almost no cardiac irregularities when injected under cyclopropane. Its selective action is shown much more on the systemic arterioles than on the automatic tissue of the heart. In the test dose it neither produced extrasystoles in the form of ventricular tachycardia nor did it whip up the sinus to abnormal rates. Only when the dose was increased four times above the equivalent test dose of adrenalin did irregularities begin to appear. From the practical standpoint neosynephrin seems to be a blood pressure raising sympathomimetic amine which can be safely used in cyclopropane anesthesia.

"Methadrin also is not selective for the ventricular automatic tissue and has little effect on the sinus rate.

"Ether does not sensitize the ventricular automatic structures to neosynephrin, cobefrin, arterenol or ephedrine. Cobefrin, arterenol and ephedrine, however, increase the sinus rate.

"Under chloroform, neosynephrin had little effect, nodal extrasystole being seen but once. Both cobefrin and arterenol gave more irregularities and each caused one ventricular tachycardia. Ephedrine produced no ventricular rhythms of any kind. From these experiments we must conclude that some degree of ventricular sensitization is produced by chloroform for cobefrin and arterenol. As already seen, the same is true for adrenalin.

"The five amines which regularly produce multifocal tachycardia under cyclopropane have one thing in common, the catechol ring. Although this ring may have much to do with intensity it does not determine specificity, for catechol itself is inactive and the amines without it will bring on irregularities if the dose is made large enough.

"Although barbital sodium protects against the cardiac effects of ephedrine or of cyclopropane separately, barbital sodium or pentobarbital sodium gave no protection whatever against the combined effect of blood pressure raising agents and of cyclopropane. It is possible that amytal gave some protection.

"Excess carbon dioxide in moderate amounts does not have great influence on cardiac irritability.

"Both before and during ventricular tachycardia induced by the injection of blood pressure raising agents the oxygen content of the blood was high. It is therefore almost certain that the cardiac irregularities following cyclopropane anesthesia alone depend fundamentally in some way on the cardiac action of the anesthetic rather than on systemic anoxemia. If anoxemia is present, they are thereby favored, and often in both experiment and clinical practice they may be abolished by ventilation with oxygen. If the concentration of the gas is increased they will appear again even with abundant oxygen.

"Cannon has estimated that the reflex secretion of adrenalin might reach 0.005 mg. per kilogram per minute. On this basis our test injection would be only twice the possible maximal reflex secretion. In addition some animals have responded with as little as half the test dose of adrenalin. All this seems to indicate that we may be basing our conclusions on doses within or closely approaching the physiologic range.

"Although it is stated that cyclopropane sensitizes the automatic tissue of

the ventricle to adrenalin, this action need not be a direct one. The possibility should not be overlooked that the anesthetic acts on midbrain centers which in turn influence the heart." Bibliography—4 references.

J. C. M. C.

S. KREININ, F. A. HAMBLEN and L. PORCELLI. *The Effect of Sulfanilamide on the Cross Matching of Blood.* J. Lab. Clin. Med. 25: 690–692 (April), 1940.

It seems that the inability to cross match blood following the administration of sulfanilamide is due to changes in the blood brought about by the disease and not to any change brought about by sulfanilamide.

A. S.

M. M. STRUMIA, J. A. WAGNER and J. F. MONAGHAN. *The Use of Citrated Plasma in the Treatment of Secondary Shock.* J. A. M. A., 114: 1337–1341 (April 6), 1940.

"This paper is concerned with offering evidence of the effectiveness of human blood plasma in the treatment of secondary shock. . . . Substitutes to blood transfusion in the treatment of secondary shock have so far generally failed. . . . In the present work citrated plasma was used exclusively. Details for the separation of plasma are given elsewhere. Briefly, blood is mixed with a 2 per cent. solution of sodium citrate in physiologic solution of sodium chloride in the proportion of 100 cc. of citrate-saline solution to 500 cc. of blood. Plasma is separated by suction after centrifugation and may be used fresh or stored at 4° C. after addition of merthiolate solution 1:10,000. Practically, at the Bryn Mawr Hospital most of the plasma is a by-product of the blood bank. At the end of five days of preservation the plasma is separated, pooled and stored. No cross matching is necessary, but of course each lot is tested serologically by means of the Wassermann and Kahn tests. . . .

"Routine treatment for shock . . . consists essentially of placing the patient in the Trendelenburg position, the application of heat, the administration of a narcotic and usually the intravenous administration of physiologic solution of sodium chloride with 5 per cent. dextrose. This routine treatment, without the intravenous administration of plasma or whole blood, has on many occasions proved insufficient in the treatment of shock. Concerning the dosage, it may be generally stated that it must be sufficiently large to relieve entirely the symptoms of shock. The average dose is about 500 cc., but larger doses may be necessary in cases of severe involvement. The size of the patient and the severity of the circulatory deficiency are the factors determining the size of the dose. The speed of administration depends also to a certain extent on the condition of the patient. It may be stated that it is safe to administer plasma by the gravity method, a gage 19 needle being used as fast as it will run, approximately 10 cc. a minute. We prefer generally to use the plasma diluted with an equal amount of saline-dextrose solution; this is, however, not essential. Heating of the plasma in any way is to be carefully avoided. Administration of cold plasma does not cause any reaction. For other details concerning the use of plasma the reader is refered to our previous paper. . . .

"The intravenous administration of citrated blood plasma has proved to be an ideal means of restoring an adequate blood circulation in patients suffering from secondary shock, rapidly relieving the clinical manifestations. . . . The advantages offered by citrated blood plasma are that: (*a*) it can be readily prepared and safely transported, (*b*) it can be stored for an

indefinite period of time, (*c*) it is entirely safe and free from reactions, (*d*) it can be used in large and repeated doses, (*e*) it is ready for instant use, and (*f*) it does not add to concentration of erythrocytes if this condition is present." Bibliography—34 references.

J. C. M. C.

J. O. FRENCH, M. L. HOOKER, R. B. VAUSE and A. L. ROBINSON. *Dental Anesthesia in Children, a Comparison of Vinyl Ether and Ethyl Chloride in a Series of 200 Cases.* Brit. Med. J. No. 4132, 432–435 (March 16), 1940.

A series of 200 children were given anesthesia under similar conditions, for extraction of teeth with vinyl ether or ethyl chloride. The authors believe that these are both safe and useful anesthetics; that the action of vinyl ether is shorter and less certain than that of ethyl chloride but is a useful agent for these short anesthesias in young children. Vinyl ether in this series caused more struggling during induction, more troublesome salivation, but produced less rigidity of the jaw and a rapid emergence from anesthesia. Ethyl chloride caused more rigidity of the jaw, but is more certain in its action. It has a longer recovery period and a higher incidence of post-anesthetic nausea and vomiting.

A. S.

S. O. LEVINSON, FRANK NEUWELT and HEINRICH NECHELES. *Human Serum as a Blood Substitute in the Treatment of Hemorrhage and Shock.* J. A. M. A. 114: 455–461 (February 10), 1940.

"The World War afforded an unusual opportunity to study and treat traumatic hemorrhage and shock. This resulted in a great impetus to the use of fluids intravenously for restoring normal fluid balance, combating hemorrhage and resultant shock, and aiding the treatment of wound septicemias and toxemias. At present infusions are also used widely for anemias, burns and dehydration due to various causes. Blood has been the fluid of choice in practically all conditions. However, on reflection it appears that blood may be replaced quite adequately in some circumstances. Thus, in severe infections serum (other than specific serum) may be used instead of blood if there is no associated secondary anemia. Traumatic and operative shock and burns are characterized by extensive plasma loss and hemoconcentration, resulting in a diminished volume and more viscid blood. It would seem that these conditions would be best relieved by serum or saline solution, which not only reestablish normal blood volume but also reconstitute normal plasma cell ratios. It is still believed that whole blood cannot be replaced in the infusion treatment for anemia, because of the need for red blood cells. It is likewise thought that severe hemorrhage, in which all the constituents of the blood are lost, can be treated only by the restoration of whole blood. Although whole blood is undeniably the ideal restorative fluid, the question may well be raised if it is the only fluid that can be used and if there may not be an adequate substitute which offers advantages over blood.

"It may be stated briefly and categorically at this point that the loss of erythrocytes in severe hemorrhage is seldom a vital factor. The sudden and marked diminution in circulating blood volume is of grave and serious significance because this oligemia leads to rapid development of secondary shock as a result of anoxemia. . . . It is quite apparent that delay in instituting treatment is a serious matter, for the degree of shock increases and may become profound and irreversible. All blood transfusions must be preceded by cer-

tain laboratory procedures: (1) typing the patient, (2) typing a proper donor, (3) careful testing for compatibility and (4) performing Kahn or similar tests. . . . Hence a serious drawback in the use of blood transfusion as an emergency measure is a certain unavoidable delay of varying duration. It was this delay, in addition to other considerations such as frequent difficulty in securing blood for indigent patients, that led to the development and the use of 'stored' or 'preserved' blood. . . . Reactions following blood transfusions are still relatively frequent. The most serious type of reactions is those due to hemagglutination or hemolysis. . . .

"The use of serum or plasma infusions for combating the effects of hemorrhage, considered as far back as 1918, has again been proposed in recent publications. Serum can be prepared for immediate use and large amounts of pooled serum can be administered without adverse reactions. This study was therefore undertaken to determine whether whole blood could not be replaced effectively by serum and how the latter compared with various crystalloid infusions in the treatment of hemorrhage and resultant shock. The dog was used because its physiologic behavior is similar to that of man in these conditions. Dog plasma forms fibrin clots or 'veils' and becomes very cloudy. It was difficult to remove this material, for even after filtration there was a tendency for reformation of the fibrin veil. These fibrin particles and veils resembled the growth from bacterial contamination and required repeated sterility tests. Dog serum instead of plasma was employed, thereby avoiding these difficulties.

"Experiments were performed on anesthetized dogs (pentobarbital sodium) weighing from 13 to 22 kg., in which blood pressure was recorded in the usual way. A femoral artery was prepared for bleeding and a femoral vein for infusions. After a control blood pressure had been recorded, the animal was bled rapidly until its blood pressure fell to shock level (systolic pressure of 40–60 mm. of mercury). The blood pressure was maintained at shock level for periods varying from ten to twenty minutes before an infusion of either saline solution or dog serum was given. The amount of fluid administered varied from one fourth to several times the amount of blood removed. Eight such experiments were done, and all of them demonstrated superiority of blood serum over saline solution as an infusion medium following hemorrhage and shock in dogs. . . .

"The procedures are described in detail here because they were used in all further experiments. A considerable section of the right carotid artery was freed and the right jugular vein exposed aseptically under light ether anesthesia. Wide glass cannulas were inserted in both vessels. Three hours were then permitted to elapse to allow the effects of anesthesia to wear off. At the onset of each experiment pulse, respiration and temperature were recorded. . . . A determination of the circulating blood volume was made . . . ; arterial blood was drawn from the cannulated carotid artery for red blood cell count and hemoglobin as well as for determination of carbon dioxide, oxygen, chlorides, nonprotein nitrogen and plasma proteins. The animal was then bled until it was reduced to a state of shock as judged by blood pressure readings as well as by its clinical condition.

"Our aim in these experiments was to produce a state of post-hemorrhage shock by a single massive hemorrhage, leave the animal in this condition for two hours so that increased capillary permeability and secondary shock might develop, and then transfuse with various fluids. It was found that a

number of animals recovered to a varying degree in the two-hour period, while others remained in shock, and therefore transfusions with saline solution, serum or blood gave varying and inconsistent results. It is worth noting that those dogs having the highest blood pressures at the conclusion of the experiment had received either blood or serum. Another interesting feature was that the blood proteins remained at normal levels following serum infusions, whereas they showed considerable diminution after saline infusion. In one experiment with saline solution the serum protein level fell to 3.6 per cent. per hundred grams, a dangerously low level. . . . The method of massive hemorrhage and delayed infusion therapy having failed to produce a consistent and maintained shock simulating the condition frequently encountered in man, we resorted to another approach. A state of shock was induced gradually by repeated periodic bleeding and delayed subsequent infusions. During this process the blood reserves were so depleted that they played a less significant role in recovery and survival. . . .

"Twenty-eight experiments were performed. Five dogs were reinfused with their own citrated whole blood removed at preceding bleedings. Twelve animals were reinfused with serum from other dogs. Nine dogs were given saline infusions, four receiving physiologic solution of sodium chloride and five receiving Hartmann's solution, with or without 2 per cent. dextrose. Two control experiments were performed in which no restorative fluids were given. . . . We realized soon that this procedure of graded bleedings was the proper approach to study differences in the effects of the infusion fluids. All dogs that were bled four times, with removal of 80 per cent. (30, 20, 20 and 10 per cent.) of the calculated circulating blood volume and were given infusions either of whole blood or of blood serum, survived. Dogs given infusions either of saline solution or of Hartmann's solution died during the course of the experiment; one died after the second bleeding (50 per cent.), three after the third bleeding (70 per cent.), and the remaining five died from ten minutes to two and one-half hours after the second bleeding. . . . In the beginning of the experiments the control blood pressures of all animals were approximately the same . . . ; they fell to a varying degree after the first bleeding. . . . A particularly low figure was obtained in a splenectomized dog. Marked variation in response to hemorrhage is to be expected on the basis of varying degrees of vasoconstriction, blood reserves and general condition of the animals. One half hour after the first bleeding . . . only seven of the dogs were suffering from various degrees of shock, their blood pressures ranging from 60/35 to 95/65 mm. of mercury. The first infusion was then given and the blood pressure rose to normal levels . . . in all but four instances. In these, serum had been used and was followed by a 'reaction' in which the blood pressure remained the same or was depressed to shock levels. This 'reaction' was transient, occurred only after the first infusion of serum, and subsequent infusions of the same lot of serum gave no further unfavorable effect. All the blood pressures were approximately normal half an hour after the first infusion. . . . From this point on, however, unmistakable differences began to appear between the different groups of animals. The most noticeable drop in blood pressure occurred in the saline animals following the second bleeding. . . . At the end of the experiments the average blood pressures in those saline animals still alive was at shock levels, whereas the blood pressures of the blood and serum dogs,

although reduced from their original levels, were quite satisfactory.

SUMMARY OF EFFECT OF TRANSFUSION FLUIDS

"*Saline Solution.*—The animals derived only partial, temporary and progressively diminishing restorative effects from this fluid. There were progressive fall in blood pressure, increasing acidosis, diminishing plasma protein, diminishing red blood cells and a progressive state of shock terminating in death in all instances.

"*Serum.*—The benefits from this fluid were strikingly good and permanent. Blood pressures were well maintained, alkali reserve and plasma proteins remained normal, shock was effectively combated, and all animals survived. The red blood cells and the hemoglobin were markedly diminished, but no animals showed any serious effects from this anemia and their general condition was surprisingly good at the end of the experiment.

"*Blood.*—This fluid was the best but aside from cell replacement was in most respects not superior to serum. The animals in this group all survived and showed only minor blood pressure decreases and weakness from the prolonged experiment. . . .

LIMITS OF BLEEDING AND INFUSION

"We were interested in determining to what extent animals could be bled and reinfused with serum and blood beyond the 80 per cent. blood removal and replacement described. Two 'whole blood' experiments were performed. In the first animal 140 per cent. of the circulating blood volume was removed and reinfused. The final blood pressure was 125/115, compared with an initial pressure of 170/120; the alkali reserve, blood volume and hemoglobin remained relatively constant. The other animal was subjected to 150 per cent. blood removal and replacement in stages; the final blood pressure was 125/95, while the original blood pressure had been 170/110. Alkali reserve, blood volume and so on showed insignificant changes. Both dogs remained in good condition, although somewhat exhausted by the prolonged experiment. . . . Two dogs were bled and infused as usual until 80 per cent. of the blood had been removed; then 10 per cent. bleedings and reinfusions were continued until 110 per cent. and 140 per cent. of the blood had been removed before these animals died. Both animals were in fair condition until the last 10 per cent. bleeding, following which the blood pressure fell markedly and the animals died before the next infusion period. The hemoglobin was reduced from 118 and 116 per cent. to 25 and 24 per cent. respectively and the arterial oxygen content fell proportionally; acidosis did not develop until terminally.

"Similarly two other dogs were bled and given infusions of serum until 120 per cent. of the calculated total blood volume had been removed. In one dog the blood pressure dropped with successive bleedings but rose following the serum infusions. At the end of the experiment the blood pressure was 95/50 and the animal was in fair condition. Hemoglobin fell from 138 per cent. to 34 per cent. and the pulse rate increased from 88 to 188 beats per minute. Blood carbon dioxide after the 110 per cent. bleeding was 37.6 volumes per cent. The other dog had a blood pressure of 145/90 reduced from 119 per cent. to 63 per cent. The animal withstood four additional bleedings, at the conclusion of which the blood pressure was 115/60 and the hemoglobin 42 per cent. A total of 1,200 cc. of blood had been removed and replaced by an equal quantity of serum. Actually the loss of blood was somewhat higher, approximating a total of more than 1,400 cc. At the start of

the experiment the animal's circulating blood volume as measured was 1,057 cc., with plasma volume of 624 cc. and a cell mass of 433 cc. Before the fourth bleeding, after 70 per cent. removal of blood, although the plasma volume had remained constant, the cell mass had fallen to 160 cc., about 37 per cent. of the original. The circulating cell mass at the conclusion of the experiment was much lower than the latter figure. Yet after such extensive removal of blood and depletion of red blood cells the dog was relatively strong and well, not acidotic and apparently little disturbed by his extreme anemia, for the pulse had increased only from 96 to 142 per minute. This experiment illustrates not only the restorative effect of serum but also the exceptional vitality of some dogs. . . .

REACTIONS

"The nature of the serum 'reaction' mentioned, which was encountered in about 25 per cent. of serum infusions, was of unusual character. The only constant sign of reaction was a moderate and transient drop of blood pressure, from which the animals always recovered spontaneously within the one half hour post infusion period. Further infusions of the same serum into the same animal never brought a repetition of this effect. Occasionally there were additional symptoms, such as chilling, growling, vomiting and defecation, which likewise were of transitory nature and did not recur on subsequent serum infusions. The same pool of serum would cause reactions in one animal and not in others. Compatibilities were performed in all instances, and only compatible serum was used. We were unable to establish a common causative factor, and this subject is now being further investigated with reference to sensitivity and other factors. . . .

COMMENT

"Our experiments have demonstrated that serum overcomes all the effects of hemorrhage in dogs except the loss of red blood cells. . . . If serum is as effective in overcoming the effects of hemorrhage in man as it appears to be in dogs, then certainly it would provide the ideal substitute at the battle front. Since serum requires no particular care in handling and no preliminary testing and may be preserved for a long time, it can be processed in ample quantities from the blood of noncombatants in civilian centers far removed from the war front, prepared in proper containers ready for use and distributed directly to the front, where it can be stored until used. . . . We have had the opportunity to employ pooled human serum in a limited number of cases of hemorrhage or shock. The effects from immediate human serum infusion on the blood pressure and general condition in these cases paralleled the beneficial results observed in our animal experiments." Bibliography—25 references.

J. C. M. C.

E. L. DEGOWIN, J. E. HARRIS and E. D. PLASS. *Studies on Preserved Human Blood. I. Various Factors Influencing Hemolysis.* J. A. M. A. 114: 850–855 (March 9), 1940.

"The current interest in the use of preserved human blood for transfusions has been especially motivated by economic pressure in the United States and by military necessity in Europe. Hence the empirical clinical use of transfusions of preserved blood has tended to precede rather than to follow fundamental objective biologic and chemical studies in the laboratory. A review of the literature reveals few data from which the clinician can establish satisfactory criteria for the use or rejection of preserved blood. . . .

There is considerable evidence that the intravenous injection of a large amount of hemolyzed blood may result in death, but the exact relation of hemoglobin to the production of severe transfusion reactions has not been determined. . . . The object of the studies here reported was to determine the rates of hemolysis occurring in human blood in various preservatives and stored under a variety of conditions. . . .

"In the majority of the experiments the general procedure was the same. Erlenmeyer flasks or pyrex glass of from 1,000 to 1,500 cc. capacity were autoclaved with appropriate amounts of the preservative to be studied. When dextrose solutions were to be combined with other chemicals, the former were heated separately to avoid caramelization and later combined with the latter aseptically. Blood was drawn into the flasks from the median basilic veins of healthy men in quantities of from 400 to 600 cc. The blood was mixed with the preservative by gentle rotation of the receiving flasks. A 16-gage needle was used and connected to the flask by a 15-inch section of gum rubber tubing. Before the cells settled, the entire mixture was apportioned in 50 cc. quantities into 250 cc. Erlenmeyer flasks closed with cotton plugs. The entire lot was stored under identical conditions, and when an analysis was to be made the entire contents of one small flask were thoroughly shaken and the cells were centrifuged out. The supernatant plasma was then pipetted off and analyzed for hemoglobin. This procedure insured a uniform dilution of blood and preservative throughout the entire experiment and obviated the difficulties attendant on sampling the same flask repeatedly.

"The refrigerator used was a room cooled by open coils of salt brine. The temperature was maintained at from 3° to 5° C. by an electrically controlled thermostat. Continuous records of the temperature were kept. The frost on the open refrigeration coils insured a high relative humidity and thus a minimum of evaporation.

"Special precautions were taken to keep the blood away from sunlight or from prolonged exposure to artificial light. . . .

"The following solutions were used in preservatives: 5.4 per cent. anhydrous dextrose U.S.P. (Merck & Co., Inc.) in distilled water, 5.4 per cent. anhydrous dextrose (Eastman Kodak Company) in distilled water, 3.2 per cent. sodium citrate (Merck reagent grade, $Na_3C_6H_5O_7\ 2H_2O$) in distilled water (sterilized by Berkefeld filtration).

"Several methods of estimation of small amounts of hemoglobin were tried before final adoption of the method of Wu. This is a quantitative application of the benzidine test for hemoglobin in which a brown compound is compared in the colorimeter with a similar color developed in a standard hemoglobin solution. . . .

"Many of the facts demonstrated in the laboratory have been applied in the routine operation of the blood bank in the University Hospitals. . . . Criteria for determining when preserved blood becomes unfit for use cannot be presented accurately. From experience we have adopted the arbitrary rule that citrated blood should be discarded after ten days of storage and blood in the dextrose-citrate mixture is considered unfit for transfusion after thirty days. With this practice there have been no unusual reactions which could be ascribed to distintegrated blood and no hemoglobinuria. The oldest blood used was transfused after storage in dextrose-citrate mixture for thirty-eight days. The recipient suffered no reaction, and no hemoglobin appeared in the urine. In the operation of a blood bank where the daily number of transfusions is large the need for a preserva-

tive in which blood can be stored for more than seven days is not urgent. If the number of transfusions is not large, however, a proportionately larger loss is incurred among bloods belonging to the rarer groups AB and B. In a blood bank which averages four transfusions daily the mathematical probability that a blood of group AB or B will be required within seven to ten days is not great. Therefore any preservative which can prolong the period of potential usefulness of such a blood results in smaller losses.

". . . Progressive hemolysis occurs in human blood stored in any of the preservatives studied. . . . The rate of hemolysis is much greater when blood is stored at 20° C. than at 5° C. . . . The addition of large quantities of isotonic dextrose solution to blood slows considerably the rate of hemolysis as compared with that in blood stored with little or no added dextrose. . . . The Rous-Turner blood-dextrose-citrate mixture has been so modified that it can safely be given intravenously without discarding the plasma. This modification consists of ten volumes of blood, thirteen volumes of 5.4 per cent. aqueous solution of anhydrous dextrose and two volumes of 3.2 per cent. dihydric sodium citrate in water. . . . Blood stored in the modified blood-dextrose-citrate mixture will hemolyze only one twenty-fifth to one fiftieth as much in thirty days at 5° C. as will blood in sodium citrate alone or in sodium citrate plus sodium chloride. . . . The blood-dextrose-citrate mixture has proved safe and practical for human transfusions and is of distinct advantage in the operation of blood banks with a small volume of transfusions. . . . Hemolysis is less in blood stored in sealed flasks from which the air is completely displaced by the blood mixture than when the blood is exposed to the air. . . . Blood stored in flasks containing air trapped by rubber stoppers hemolyzes no faster than blood exposed to the air in cotton-plugged flasks. . . . Erythrocytes stored in the dextrose-citrate mixture resist destruction by shaking better than do those stored in sodium citrate alone or in citrate-saline mixtures. . . . The initial hemolysis encountered when blood is drawn into large volumes of preservatives can be prevented if the blood is cooled rapidly and uniformly by mixing it with preservatives which have been previously cooled to about 5° C. Bibliography—12 references.

J. C. M. C.

E. L. DEGOWIN, J. E. HARRIS and E. D. PLASS. *Studies on Preserved Human Blood. II. Diffusion of Potassium from the Erythrocytes During Storage.* J. A. M. A. 114: 855–857 (March 9), 1940.

"The concentration of potassium in the human erythrocyte is normally from seventeen to twenty times that in the serum. Any change in this ratio occurring during the storage of blood is of clinical interest in view of the well known toxicity of potassium salts injected intravenously. . . . The studies here recorded were undertaken with the hope that the increase in plasma potassium might serve as an index of corpuscular deterioration. . . . For each analysis a flask containing 50 cc. of blood mixture was withdrawn from storage, the contents were thoroughly shaken and centrifuged, and the plasma was pipetted off for analysis. This procedure insured a constant proportion of cells and plasma in all specimens of a series derived from any initial blood mixture. Estimations of the plasma potassium were made by the silver cobaltinitrite method of Truszkowski and Zwemer. Analyses were made in triplicate and were compared with duplicate standards. The deviation from the mean in these determinations was generally less than 2 per cent. The

possibility that ammonia contributed to the observed values was excluded by comparing plasma filtrate with ashed samples. The data presented agree in general with those reported by Scudder and his associates. Certain apparent discrepancies may be explained by differences in experimental procedure.

CONCLUSIONS

"(1) There is progressive diffusion of potassium from human erythrocytes into the plasma during storage. (2) This diffusion is rapid during the first five days but becomes gradually less. A maximum concentration of potassium in the plasma is approached in from fifteen to twenty days. (3) The high values of plasma potassium attained in from fifteen to thirty days of storage cannot be accounted for by the release of that ion from completely hemolyzed cells. (4) Variations in the content of sodium, chloride, citrate and dextrose in the preservative mixtures or storage at different temperatures and in various atmospheres did not affect the diffusion rate." Bibliography—11 references.

J. C. M. C.

E. L. DEGOWIN, R. C. HARDIN and J. E. HARRIS. *Studies on Preserved Human Blood. III. Toxicity of Blood with High Plasma Potassium Transfused into Human Beings.* J. A. M. A. 114: 858–859 (March 9), 1940.

"In a previous paper it was shown that some of the potassium in the erythrocytes of human blood diffused out during storage and that the maximum concentration of that ion in the plasma was approached in fifteen days. The rate or the amount of diffusion was not affected by the type of preservative used or the other conditions of storage studied. The question arose as to whether blood stored for two weeks or more would be toxic when transfused into human beings. Some clinical evidence existed indicating that such blood was not harmful. . . . The object of this study was to ascertain whether preserved blood stored long enough to attain maximum concentration of potassium in the plasma was toxic when transfused into human beings under the usual clinical conditions. From data presented in another study it was evident that blood must be used which had been stored fifteen days or longer to attain the maximum concentration of plasma potassium. It had also been shown that a practical method of preserving blood for that length of time without extensive hemolysis was the use of a mixture of ten volumes of blood, thirteen volumes of 5.4 per cent. dextrose in water and two volumes of 3.2 per cent. dihydric sodium citrate in water. This dilution of the plasma reduced the concentration of the potassium per cubic centimeter by about two thirds the value obtaining in citrated blood of the same age, but the total amount of the ion in the plasma was approximately the same in the two mixtures since it was derived from the erythrocytes of 500 cc. of blood in both cases. Transfusion of citrated blood stored for fifteen days was considered too dangerous because of the high content of hemoglobin in the plasma, but such mixtures stored for ten days were used in some cases since the concentration of potassium per cubic centimeter of plasma was higher than in the more dilute dextrose-citrate mixture.

"Fourteen patients requiring transfusions were given preserved blood by the usual technic of intravenous administration. In none was there clinical or electrocardiographic evidence of heart disease. Precautions were taken to insure the urine being alkaline before transfusion by the administration of sodium bicarbonate if necessary. The blood mixture was allowed to run into the vein of the recipient by grav-

ity. The velocity was varied by adjusting the height of the column of fluid and by using needles of two calibers, 16-gage and 20-gage. The preserved blood was not heated to body temperature before injection. Immediately before, in the middle and at the conclusion of each transfusion blood specimens were withdrawn from the opposite arm of the recipient. A sample was also taken from the last 20 cc. of transfusion mixture remaining in the apparatus. Quantitative estimations of plasma or serum potassium were made in duplicate on each sample, using both a modification of the silver cobaltinitrite method of Truszkowski and Zwemer, . . . and also the chloroplatinate method of Consolazio and Talbott with slight modification. The values obtained by the two procedures gave satisfactory checks, so that only the results by the silver cobaltinitrite method are published here. When the blood samples were withdrawn from the recipient, electrocardiographic tracings were made with the three standard leads. . . . No unusual clinical reactions were observed except for the appearance of generalized urticaria in case 1. Electrocardiograms during this transfusion showed tachycardia, which was attributed to the necessary scratching due to the pruritis. In a large series of transfusions of preserved blood no evidence has been obtained to attribute the occasional incidence of urticaria to the high potassium content of the plasma. There were no alterations of the electrocardiograms of the other thirteen recipients during transfusion. The velocity of injection in different experiments varied from 6.6 to 43.3 cc. of blood mixture per minute. Two of the recipients . . . had slightly elevated initial serum potassium values and one . . . had a low level before transfusion. The highest concentration of plasma potassium in transfused blood was 148 mg. per hundred cubic centimeters, and this was given at the rate of 41.6 cc. of blood mixture per minute. The rise in serum potassium of the recipients during transfusion never exceeded 2.2 mg. per hnndred cubic centimeters and was not accompanied by any symptoms. . . . The high plasma potassium content in blood preserved for thirty days is not toxic when the blood mixture is transfused into human beings at velocities of less than 43.3 cc. per minute. The concentrations of plasma potassium encountered in blood stored for one month are not high enough to cause significant increases in the serum potassium of the recipient." Bibliography — 8 references.

J. C. M. C.

E. L. DEGOWIN, R. C. HARDIN and L. W. SWANSON. *Studies on Preserved Human Blood. IV. Transfusion of Cold Blood Into Man.* J. A. M. A. 114: 859–861 (March 9), 1940.

"It is still common clinical practice to maintain at body temperature fluids which are being administered intravenously. This probably originated from clinical dicta which preceded the fundamental work of Seibert on pyrogenic substances. A rough calculation can be made showing the effect which the intravenous injection of a cold solution would have on the body temperature if the heat regulatory mechanisms were suspended, and the assumption is made that the thermal capacity of the parenteral fluid is the same as that of the body tissues. A simplified formula expressing the physical principle of equal heat exchanges can then be stated: $M_1(t_1 - t) = M_2(t - t_2)$ where M_1 is the mass of parenteral fluid injected, M_2 the body weight, t_1 the temperature of the fluid, t_2 the original body temperature, and t the resultant temperature of the transfused body. If one takes a specific clinical problem, when 600 cc. of fluid at 5° C. (41° F.)

is injected intravenously into a man weighing 70 Kg. and having a temperature of 37° C. (98.6° F.) the following equation results: $0.6\ (5-t) = 70\ (t-37)$, or $t = 36.72°$ C. The body temperature would then be reduced by only 0.28° C. This conception is of practical clinical importance because considerable labor is expended by the intern and nursing staff and frequently costly apparatus is used in an effort to maintain parenteral fluids at body temperature during injection. . . .

"The problems introduced by the use of preserved blood for transfusions make imperative a study of the effects of injecting fluids at room temperature or lower. . . . A study of the effects of transfusion of unheated blood was made. This study was divided into two parts: first, detailed observations on ten patients receiving transfusions, and, second, a careful check of all patients receiving transfusions of cold preserved blood in the University Hospitals for a period of eleven months.

". . . A detailed study of ten patients who were given transfusions of blood mixtures varying from 25° to 15° C. and at velocities from 6.0 to 42.8 cc. per minute revealed no significant lowering in the body temperature, no consistent changes in blood pressure and no untoward clinical symptoms. . . . Preserved blood has been administered without preheating in 568 cases with no reactions which could be attributed to the procedure. . . . The practice of transfusing preserved blood cold is a great convenience in conserving time and prevents untoward reactions involved in the process of heating it. . . . Parenteral fluids other than blood can be administered at room temperature with safety." Bibliography—6 references.

J. C. M. C.

E. PODOLSKY. *Anesthesia: The Conquest of Pain.* Am. Professional Pharmacist 5: 629–31 + (November), 1939.

The discoveries in the field of anesthesia have materially changed the possibilities for surgical advance particularly in regions of the body heretofore thought inaccessible. A review of the field, with some interesting historical and technical points.

A. S. [redacted]

C. B. ODOM. *Epidural Anesthesia in Résumé and Prospect.* Current Researches in Anesth. & Analg. 19: 106–108 (March–April), 1940.

"Epidural block, which derives its name from the space into which the anesthetic solution is injected, was devised by a young Spanish Army surgeon in 1920. . . .

"I feel that the negative pressure technique, first introduced by Gutierrez and modified by us with the use of the glass indicator and special needle, has definite advantages and is far safer than the method advocated by Dogliotti and his co-workers.

"In recent months we have made serial radiographs of patients following the epidural injection of a 2 per cent. novocain solution in lipiodol. The diffusion of this opaque oil has demonstrated conclusively how the anesthetic solution injected into the epidural space effects a block. The X-rays taken immediately following the injection show the oil within the epidural space in the spinal canal. At this stage there is no anesthesia. A few minutes later the oil has begun to diffuse out of the epidural space through the intervertebral foramina along the perineural sheaths. Anesthesia begins to set in. At the end of fifteen minutes the nerve roots are outlined by the lipiodol. When this has occurred the block has been accomplished. By the time thirty minutes have elapsed the greater part of the oil has left the epidural space and has spread out along the nerve roots.

"By analysis of spinal fluid taken from a case while an epidural block was in effect it has been possible to show that novocain was absent from the fluid. This demonstrates that the novocain solution injected into the epidural space does not penetrate the dura and diffuse into the spinal fluid. Since this is true, it is impossible for the anesthetic solution to block the nerve root until it has left the epidural space and entered the paravertebral region, for the dura is continued as a covering of the nerve roots to just outside the intervertebral foramina.

"On these findings it is possible to explain some of the cases of incomplete block, for it has been demonstrated in some of the X-rays that occasionally there is an obstruction at one or more intervertebral foramina, probably due to adhesions or anatomical anomalies preventing the outward diffusion of the anesthetic solution. Because the solution does not come in contact with these roots, an incomplete block results. . . .

"We have treated almost 100 cases of sciatica by injecting 10 to 15 cc. of a 2 per cent. solution of novocain in almond oil into the lumbar epidural space with excellent results. . . . We also have used pantocain in a base of almond oil and A.B.A. solution composed of anesthesine 3 per cent., ether 1 per cent., benzyl alcohol 5 per cent. in oil of sweet almond, for epidural injection to relieve pain.

"Several cases of intractable pain from generalized carcinomatosis have been given injections of 10 to 15 cc. of 95 per cent. alcohol. There was only a partial relief of pain in these cases but it is interesting to note that the alcohol caused no demonstrable ill-effects and that in none of the cases did a muscular paralysis result.

"Angina pectoris is another condition in which we have been able to relieve pain. This is accomplished by injecting 10 cc. of 2 per cent. novocain in almond oil into the epidural space between the seventh cervical and first thoracic vertebrae. It is surprising the ease with which the space can be localized at this level by using the negative pressure technique. I have also used this high epidural block for the relief of two other conditions. The first was substernal pain due to an aortic aneurysm in a Negro woman. . . . I administered 10 cc. of 2 per cent. novocain solution in almond oil into the epidural space and completely relieved her pain. She was allowed to return home and has been returning at three-week intervals to have the block repeated. As soon as the pain returns she comes in for another block. Another interesting group relieved by this high epidural block includes a number of asthmatics who were having severe prolonged seizures which could not be relieved by adrenalin, aminophyllin, morphin or oxygen tent. In these the spasm of the bronchials was relaxed by epidural injection of 10 cc. of 2 per cent. novocain solution into the epidural space. This effect is difficult to explain, in that the block could have no effect on the parasympathetics. . . .

"Two facts have made themselves evident from the cases we have treated. *First*, there are definite possibilities in epidural block which have not been explored, and *second*, the space will tolerate, with little or no untoward effect, the injection of a number of different types of solutions." Bibliography—9 references.

J. C. M. C.